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.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk factors for emergence agitation during the awakening period in elderly patients after total joint arthroplasty: a retrospective cohort study
AUTHORS	Wang, Naigeng; Hao, Jianhong; Zhang, Jie; Du, Jing; luo, zhenguo

VERSION 1 – REVIEW

REVIEWER	Eshetie, Denberu Debre Tabor University, Anesthesia
REVIEW RETURNED	27-Oct-2022

GENERAL COMMENTS	Describe the study design in the method part I think it is either a cross-sectional study or a retrospective cohort study, observation can be held for prospective studies only that used to collect primary data Use multivariable, not multivariate they are different, multivariate logistic regression analysis is when you have more than one dependent/outcome variable. While multivariable is analyzing one dependent variable with more than one independent variables. Line 59-63 Justify whether prolonged or short fasting time caused EA. The introduction part focuses on pediatrics EA than elder patients, it is not a study conducted on pediatric patients so focus mainly on your topic. Define the fasting time from the method part, when you say prolonged fasting time? It is only described in the result part. A VAS score of greater than 4 is considered as moderate pain and it is known that moderate to severe pain should be managed but your study participants' pain was managed with a VAS score of ≥ 5 could you describe why? Use the term postoperative pain than the VAS score in the abstract part (line 57-58).

REVIEWER	Jones, Gareth Imperial College London, MSk Lab
REVIEW RETURNED	15-Dec-2022

GENERAL COMMENTS	Thanks for submitting this paper, which is very clear in its objectives, methodology, and findings.

REVIEWER	Lam, Christopher M. The University of Kansas Medical Center
REVIEW RETURNED	19-Jan-2023

GENERAL COMMENTS	Dear authors, Thank you for your work and contribution to the field of anesthesia with your study. The methods and design were sound. The Conclusions were adequate based on study results. I think the discussion section was adequate and the limitations were well highlighted. I saw that you used an English editing program. However, despite this, the paper does have a lot issues with plurality and tense. Further, there are some phrases that need to be rewritten as indicated below. I think once the paper is edited and rewritten, it will read much smoother. Page 5, line 77. Replace splitting with dehiscence. Page 5, line 81. Reword strange recovery surroundings. Page 6, line 100. Very abrupt transition. You were talking about surgical risk factors for EA and then transitioned to OA. Page 6, line 101. Define “older people.” Page 6, line 104. Re word. Page 6, line 104. Again, very abrupt transition. You were talking about OA incidence and then pivoted to EA risk factors. This should be a new paragraph. Page 17, Line 295 to 298. Rephrase

REVIEWER	Kazune, Sigita University of Latvia, Institute of Atomic Physics and Spectrscopy
REVIEW RETURNED	24-Jan-2023

GENERAL COMMENTS	The main question addressed by the authors is the risk factors for emergence agitation (EA) in elderly patients who have undergone total joint arthroplasty under general anesthesia.The topic of EA is not new, but most previous studies that have examined EA have been done in children. The focus on EA in elderly patients in the context of TJA, is an original aspect of this study. However, I have several questions and comments: 1. The introduction concentrates heavily on research on emergence delirium in pediatric patients and does not clearly explain the rationale for studying emergence agitation in elderly patients who have undergone orthopedic surgery. Summary of recent research on EA in adult and elderly patients is needed so that existing knowledge gaps can be easily identified by the reader. It should be rewritten. 2. Methods : This is a retrospective study. How was written consent obtained? 3. The type of general anesthesia in this study is unusual as it states that etomidate was used for induction and propofol for maintainance. This makes the results of this study difficult to generalize. This aspect needs to be highlighted in the discussion and is a serious limitation. 4. Where were the patients extubated: PACU or OR? This information should be included. 5.The choice RASS of 1 to define EA needs to be justified. Clear references should be made to other studies using the same definition. 6. What is TOA (line210)?

VERSION 1 – AUTHOR RESPONSE

Reviewer Comments:

Reviewer 1

Describe the study design in the method part I think it is either a cross-sectional study or a retrospective cohort study, observation can be held for prospective studies only that used to collect primary data

Reply: Thank you for pointing our this error. This study was a retrospective cohort study. We have updated the revised manuscript accordingly and assure you that this correction did not affect the study's results (page1,line3;page3,line47).

Use multivariable, not multivariate they are different, multivariate logistic regression analysis is when you have more than one dependent/outcome variable. While multivariable is analyzing one dependent variable with more than one independent variables.

Reply: Thank you for this suggestion. We have analysed data using the multivariable logistic regression analysis in SPSS. We apologise for this huge oversight. We have also made changes in the revised manuscript.

Line 59-63 Justify whether prolonged or short fasting time caused EA.

Reply: Thank you for your reminder. According to the multivariable logistic analysis in our study, longer fasting times for solids(95% CI:1.260–2.301) and fluids (95% CI: 1.263–2.365) were independent risk factors for EA.We have revised this section in the manuscript (page3 ,line59-60).

The introduction part focuses on pediatrics EA than elder patients, it is not a study conducted on pediatric patients so focus mainly on your topic.

Reply: Thank you for this helpful suggestion. Based on your suggestion, we have rewritten the Introduction part in the revised manuscript (page6-7,line90-111).

Define the fasting time from the method part, when you say prolonged fasting time? It is only described in the result part.

Reply:Thank you for the reminder.This part has been described in the revised edition (page9,line158-159).

A VAS score of greater than 4 is considered as moderate pain and it is known that moderate to severe pain should be managed but your study participants' pain was managed with a VAS score of ≥ 5 could you describe why?

Reply: Thank you for this comment. Previous studies have assessed pain using different cut-off point schemes[1-3]. In our study, pain was assessed using a 10 cm visual analogue scale (VAS) ruler, with values ranging from 0 to 10 (0 indicating no pain and 10 for most severe pain). A VAS score >4 is generally considered moderate pain; however, we acknowledge that values >4 and ≥5 have the same meaning because VAS scores are integers. We have replaced ≥5 with >4 in the revised manuscript to avoid misunderstanding (page8,line144).

Use the term postoperative pain than the VAS score in the abstract part (line 57-58).

Reply: Thank you for this suggestion. This part has been reworded (page3,line57).

Reviewer 3:

Page 5, line 77. Replace splitting with dehiscence.

Reply: Thank you for this suggestion. This word has been replaced with dehiscence (page5,line87).

Page 5, line 81. Reword strange recovery surroundings.
Reply: Thank you for this suggestion. We have rewritten the Introduction part in the revised manuscript (page6-7,line90-111).

Page 6, line 100. Very abrupt transition. You were talking about surgical risk factors for EA and then transitioned to OA.
Reply: Thank you for this helpful suggestion. Based on your suggestion, we have rewritten the Introduction part in the revised edition (page6-7,line90-111).

Page 6, line 101. Define “older people.”
Reply: We consulted relevant literature on this point [4-6], older people are defined as those over 60 years of age. Additionally, according to the Law of the People's Republic of China on the Rights and Interests of the Elderly, older people are defined as over 60 years old, which we have added to the revised manuscript.

Page 6, line 104. Re word.
Reply: Thank you for this suggestion. This part has been reworded (page6,line105).

Page 6, line 104. Again, very abrupt transition. You were talking about OA incidence and then pivoted to EA risk factors. This should be a new paragraph.
Reply: Thank you for this guildance. This part has been rewritten (page6,line102-107).

Page 17, Line 295 to 298. Rephrase
Reply: Thank you for highlighting this. This part has been rephrased (page17,line307-308).

Reviewer 4:

The introduction concentrates heavily on research on emergence delirium in pediatric patients and does not clearly explain the rationale for studying emergence agitation in elderly patients who have undergone orthopedic surgery. Summary of recent research on EA in adult and elderly patients is needed so that existing knowledge gaps can be easily identified by the reader. It should be rewritten.
Reply: Thank you for this helpful suggestion. Based your suggestion, we have rewritten the Introduction part in the revised edition (page6-7,line90-111).

Methods:
This is a retrospective study. How was written consent obtained?
Reply: The study obtained consent to gather the patient's medical record information through telephone follow-up. We have included this sentence in the revised manuscript (page7,line119-120).

The type of general anesthesia in this study is unusual as it states that etomidate was used for induction and propofol for maintainance. This makes the results of this study difficult to generalize. This aspect needs to be highlighted in the discussion and is a serious limitation.
Reply: Thank you for your guidance. This study was conducted at a single-centre where the anaesthesia measures for total joint arthroplasty (TJA) were formulated based on literature and clinical practices. The anaesthesia method and anaesthetics in our study met the requirements of the centre. Hence, etomidate was selected for intravenous induction of anaesthesia because of its favourable hemodynamic profiles, especially in elderly patients [7-9]. Several studies have reported that TIVA with propofol may reduce postoperative complications and postoperative opioid consumption [10-12]. In rhinoplasty, TIVA with propofol has been associated with shorter early emergence times, less bleeding, high surgeon satisfaction, and lower EA scores [13]. The lack of

multi-centre data is a shortcoming of our study. We look forward to comparing the occurrence of EA in different centres (page18,line325-327).

Where were the patients extubated: PACU or? This information should be included.
Reply: Thank you for highlighting this. The patients were extubated in the PACU, and we have included this in the revised manuscript (page8,line139).

The choice RASS of 1 to define EA needs to be justified. Clear references should be made to other studies using the same definition.
Reply: The RASS was first used by Curtis N. Sessler in 2002, and it has been widely used for assessing agitation [14]. It is a 10-point scale that progresses logically from "restless" (+1), which has no direct impact on patient outcomes, to "agitated" (+2), which includes patient-exhaler dyssynchrony, to "very agitated" (+3), with direct risk to the patient or staff through catheterization or aggressive behaviour. The highest level of agitation was "aggressive" (+4). Studies have demonstrated that patients with a RASS score >1 were considered to have EA (page8,line144-145) [15-18].

What is TOA (line210)?
Reply: We apologise for this oversight. This is a spelling error, which should be TJA (total joint arthroplasty), we have fixed this error in the revised manuscript (page12,line220).

References

1.Yi-Han W, Rong T, Jun L, et al. Dexmedetomidine combined with ropivacaine for erector spinae plane block after posterior lumbar spine surgery: a randomized controlled trial. *BMC Musculoskelet Disord*. 2022;23(1):235.
2.Liljeroth E, Karlsson A, Lagerkranser M, et al. Low-dose propofol reduces the incidence of moderate to severe local pain induced by the main dose. *Acta Anaesthesiol Scand.* 2007;51(4):460-3.
3.Boonstra AM, Schiphorst Preuper HR, Balk GA, et al. Cut-off points for mild, moderate, and severe pain on the visual analogue scale for pain in patients with chronic musculoskeletal pain. *Pain*. 2014 ;155(12):2545-2550.
4.Pippias M, Jager KJ, Caskey F, et al. Kidney transplant outcomes from older deceased donors: a paired kidney analysis by the European Renal Association-European Dialysis and Transplant Association Registry. *Transpl Int.* 2018 ;31(7):708-719.
5.Milan AM, Nuora A, Pundir S, et al. Older adults have an altered chylomicron response to a high-fat meal. *Br J Nutr*. 2016;14;115(5):791-9.
6.Malter MP, Nass RD, Kaluschke T, et al. New onset status epilepticus in older patients: Clinical characteristics and outcome. *Seizure*. 2017;51:114-120
7.Dumps C, Bolkenius D, Halbeck E, et al. Etomidate for intravenous induction of anaesthesia. *Anaesthesist*. 2017;66(12):969-980.
8.Shen XC, Ao X, Cao Y, et al. Etomidate-remifentanil is more suitable for monitored anesthesia care during gastroscopy in older patients than propofol-remifentanil. *Med Sci Monit*. 2015;1;21:1-8.
9. Lu Z, Zheng H, Chen Z, et al. Effect of Etomidate vs Propofol for Total Intravenous Anesthesia on Major Postoperative Complications in Older Patients: A Randomized Clinical Trial. *JAMA Surg*. 2022;157(10):888-895
10.Zhou LY, Gu W, Liu Y, et al. Effects of Inhalation Anesthesia vs. Total Intravenous Anesthesia (TIVA) vs. Spinal-Epidural Anesthesia on Deep Vein Thrombosis After Total Knee Arthroplasty. *Med Sci Monit*. 2018; 4;24:67-75.
11.Wong SSC, Choi SW, Lee Y, et al. The analgesic effects of intraoperative total intravenous anesthesia (TIVA) with propofol versus sevoflurane after colorectal surgery. *Medicine (Baltimore)*. 2018 ;97(31):e11615
12.Song JG, Shin JW, Lee EH, et al. Incidence of post-thoracotomy pain: a comparison between total intravenous anaesthesia and inhalation anaesthesia. *Eur J Cardiothorac Surg*. 2012;41(5):1078-82.

13.Talih G, Yüksek A, Şahin E. Evaluation of emergence agitation after general anaesthesia in rhinoplasty patients: Inhalation anaesthesia versus total intravenous anaesthesia. *Am J Otolaryngol*.2020;41(3):102387
14.Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002;166(10):1338-1344.
15 Makarem J, Larijani AH, Eslami B, et al. Risk factors of inadequate emergence following general anesthesia with an emphasis on patients with substance dependence history. *Korean J Anesthesiol*. 2020;73(4):302-310.
16 Kawai M, Kurata S, Sanuki T, et al. The effect of midazolam administration for the prevention of emergence agitation in pediatric patients with extreme fear and non-cooperation undergoing dental treatment under sevoflurane anesthesia, a double-blind, randomized study. *Drug Des Devel Ther*. 2019;13:1729-1737.
17 Boettger S, Meyer R, Richter A, et al. Delirium in the intensive care setting dependent on the Richmond Agitation and Sedation Scale (RASS): Inattention and visuo-spatial impairment as potential screening domains. *Palliat Support Care*. 2020;18(2):148-157.
18 Talih G, Yüksek A, Şahin E. Evaluation of emergence agitation after general anaesthesia in rhinoplasty patients: Inhalation anaesthesia versus total intravenous anaesthesia. *Am J Otolaryngol*. 2020;41(3):102387.

VERSION 2 – REVIEW

REVIEWER	Eshetie, Denberu Debre Tabor University, Anesthesia
REVIEW RETURNED	08-Mar-2023

GENERAL COMMENTS	Thank you for your line by line response, you have corrected well. I have only a single concern. Line 283, Add the percentage too. It is more useful for comparison than describing the number only.

REVIEWER	Kazune, Sigita University of Latvia, Institute of Atomic Physics and Spectrscopy
REVIEW RETURNED	11-Mar-2023

GENERAL COMMENTS	While I appreciate the efforts of authors to address the issues raised in the previous review, I must point out that the revisions appear rushed and lack thoroughness. There are multiple grammatical errors and inconsistencies in fonts throughout the manuscript. The conclusions presented in the abstract do not seem to accurately reflect the findings and discussion presented in the article. Additionally, the introduction has been rewritten as suggested by the reviewers, but unfortunately, it still fails to discuss the considerable body of literature and knowledge gaps on emergence agitation in adults. Overall, the revisions appear to lack coherence, which has resulted in an overall reduction in the quality of the manuscript.

VERSION 2 – AUTHOR RESPONSE

Reviewer Comments:

Reviewer 1:

Line 283, Add the percentage too. It is more useful for comparison than describing the number only.

Reply: *We are grateful for the suggestion**.**We have added percentages for comparison in the revised edition(page11,line201;page13,line240,line243;page14,line261,line262;page15,line282).*

Reviewer 4:

While I appreciate the efforts of authors to address the issues raised in the previous review, I must point out that the revisions appear rushed and lack thoroughness. There are multiple grammatical errors and inconsistencies in fonts throughout the manuscript. The conclusions presented in the abstract do not seem to accurately reflect the findings and discussion presented in the article.

Additionally, the introduction has been rewritten as suggested by the reviewers, but unfortunately, it still fails to discuss the considerable body of literature and knowledge gaps on emergence agitation in adults.

Overall, the revisions appear to lack coherence, which has resulted in an overall reduction in the quality of the manuscript.

Reply: *Thank you very much for taking your time to review this manuscript. I really appreciate all your comments and suggestions! We apologise for errors and the lack of thoroughness in the previously revised edition. We havechecked and modified grammatical errors and inconsistencies in fonts throughout the manuscipt in the present revised edition..For improving the quality of the English, we also got help from my colleagues and a professional institution (Editage). Regarding the suggestion for conclusions, we have rewritten the conclusions section in the present revised edition..After reviewing the extensive literature again, we have rewritten the introduction section. We appreciate all your comments and guidance.*