Peer Review File

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Reviewer A

Major concerns

It has been well-known that patient characteristics are strongly associated with POD incidence. The effect of postoperative analgesia is also associated with POD incidence. These factors may be not eliminated due to the small sample size of previous studies. The strength of the present article was to compare IVPCA with PCEA in a relatively large population to exclude confounding factors by using propensity score matching for factors of patient characteristics and the effects of postoperative analgesia.

Furthermore, the authors identified variables responsible for postoperative delirium by multiple logistic regression analysis. To match propensity scores for the selected factors from multiple logistic regression analysis in the present study are suggested to be the novelty of this study.

Introduction should be revised based on the two major concerns.

Reply: Thank you for your thoughtful comment. We agree to the comment of the reviewer. As you point out, we use propensity score matching to eliminate confounding factors in a relatively large population. We followed your advice and made some corrections to the Introduction.

Changes in the text: We have added some sentences in the Introduction section as “In addition, previous studies on the effects of postoperative analgesia on POD may not eliminate the effects of patient characteristic factors strongly associated with POD due to the small sample size of the study. To solve these problems, we compared IVPCA and PCEA in a relatively large population with controlled background factors. In our study, confounding factors affecting the results of multivariate analysis were efficiently removed by propensity score matching. [21] We present the following article in

accordance with the STROBE reporting checklist." (see Page 5, line 7-13)

Minor concerns:

Introduction

Various factors such as old age and preoperative cognitive decline have been reported to affect delirium during hospitalization.

Please insert "incidence" to get more clarification – "to affect delirium incidence during hospitalization."

Reply: Thank you for your advice. We have added the incidence date of delirium in non-cardiac surgery.

Changes in the text: We have added a sentence and some references to the Introduction. "In non-cardiac surgery, postoperative delirium occurs in 5-15% of patients. [4, 5]" (see Page 4, line 4-5)

Methods

L 91 The study was approved by the appropriate Institutional Review Board (IRB),…

Please delete "appropriate" which is redundant.

Reply: Thank you for your advice. However, we have modified this part according to the APM recommended format.

Changes in the text: We have fixed this part as follows: "The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of E-1462 and individual consent for this retrospective analysis was waived." (see Page 5, line 107-110)

L 105 backgrounds of VPCA and PCEA by…

What is VPCA?

Reply: We are sorry. This is our mistake. "I" is missing in this part. IVPCA is correct.

Changes in the text: We have modified "VPCA" to "IVPCA". (see Page 6, line 123)

Results

Please insert P values in Table 1 and discuss the new results.

Reply: Thank you for your advice. We analyzed the onset date and frequency of postoperative delirium. As a result, the onset of postoperative delirium was high on the 1st and 2nd days after surgery and low on the 3rd and 4th days after surgery. This result is consistent with previous reports that postoperative delirium is more likely to occur within 3 days after surgery. We have added a discussion of this result to the first paragraph of discussion.

Changes in the text:

We have revised Table 1 and Table legends. (see Page 19)

We have added the following text to the first paragraph of the discussion. "We investigated the incidence of POD in 3324 postoperative patients who underwent analgesic management with opioid PCA, and POD was noted in a total of 125 patients (3.8%); 55 patients (4.6%) with IVPCA, and 70 patients (3.3%) with PCEA. Eighty-four percent of patients with postoperative delirium developed within two days after surgery, consistent with the report by Marcantonio et al. [23]" (see Page 10, line 219-223)

Discussion

L 198 In this study, we used propensity score matching in a relatively large population to investigate whether morphine IVPCA or fentanyl PCEA was superior in developing POD.

Please clarify this sentence.

Reply: Thank you for your advice. As you point out, this sentence is not clear. We have added an explanation to this sentence to make it easier to understand.

Changes in the text: We have corrected this sentence as follows: "In this study, we used propensity score matching, to match patient backgrounds in in a relatively large population groups of patients who received IVPCA or PCEA, to investigate whether morphine IVPCA or fentanyl PCEA was superior in developing POD." (see Page 10,

line 223-225)

Line 243 Since POD significantly influences age-related complications such as preoperative cognitive decline and cerebrovascular disease, …

The following is suggested.

Since POD is significantly associated with age-related complications such as preoperative cognitive decline and cerebrovascular disease, …

Reply: Thank you for your advice. We have revised this sentence according to your recommendation.

Changes in the text: We have modified "Since POD significantly influences age-related complications such as.." to "Since POD is significantly associated with age-related complications such as..". (see Page 13, line 270)

L 247-252 Please move the part to Introduction.

Reply: Thank you for your advice. We have moved this part to Introduction.

Changes in the text: We have deleted the following sentences from Discussion and insert to Introduction.

"Previous studies on the effects of postoperative analgesia on POD may not eliminate the effects of patient characteristic factors strongly associated with POD due to the small sample size of the study. To solve these problems, we compared IVPCA and PCEA in a relatively large population with controlled background factors. In our study, confounding factors affecting the results of multivariate analysis were efficiently removed by propensity score matching. [21]" (see Page 13, line 274)

Reviewer B

It is not persuasive to draw the conclusion that IVPCA including morphine produces less POD than epidural PCA including fentanyl and ropivacaine with the design of this study. It is difficult to understand the conclusion that IVPCA does not increase the risk of postoperative delirum compare to epidurlac PCA through comparison with different drugs rather than using the same drug. It seems that

this paper was conducted under the assumption that epidural PCA causes less POD than IV PCA in surgery with the same general anesthesia, but this part is also difficult to understand.

Reply: Thank you for your professional comments. We focused on the fact that opioids are listed as one of the causes of postoperative delirium, and investigated the effects of different opioids and different routes of administration on postoperative delirium. As you point out, we hypothesize that IVPCA, which is given systemic opioids, has a higher incidence of delirium. We describe the hypothesis of this study in the Introduction.

As you point out, it is clearest to compare morphine IVPCA and morphine PCEA, or fentanyl IVPCA and fentanyl PCEA. Unfortunately, our facility uses different types of opioids for IVPCA and PCEA. As you point out, the conclusions drawn from research data are limited. This is a weakness of our research. However, we believe that some of our research data will be useful, as various institutions have been discussing their own data.

Changes in the text: not changed

Reviewer C

The authors study about risk of postoperative delirium in intravenous PCA and epidural PCA. This study is based on patients who underwent abdominal surgery. In table 3, operation time is a risk factor for POD. Operation time and postoperative pain can be differed by surgery type. Also, pre-operative pain severity would influence on post-operative pain and opioid consumption. Therefore, pre-op pain, categorization of surgery type and correlation with POD presence and opioid usage would be needed.

Reply: Thank you for your professional advice.

As you point out, the type of surgery may be related to postoperative delirium. Following your advice, we categorized the patients surveyed by type of surgery and conducted a more detailed examination. In other words, the target patients were divided into four categories according to the surgical site, and the data was analyzed again. As

a result, surgical site was not a factor associated with delirium in logistic regression analysis. We have added surgical site data to the revised text, but there was a difference in the surgical site distribution after propensity score matching. We have added this difference in the distribution of surgical sites at the end of the discussion as a limitation of our research.

Regarding preoperative pain, if there is strong preoperative pain and opioids are used, the postoperative analgesic regimen is different from usual. Therefore, such patients are not included in this study.

Changes in the text:

We have revised Table 2 and 4. (see Page 20 and 22)