Author’s response to reviews

Title: Prospective Investigation of Patient-Controlled Intravenous Analgesia with Hydromorphone or Sufentanil: Impact on Mood, Opioid Adverse Effects, and Recovery

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Title: Prospective Investigation of Patient-Controlled Intravenous Analgesia with Hydromorphone or Sufentanil: Impact on Mood, Opioid Adverse Effects, and Recovery

Correspondence Author: Zhiying Feng

Dear Editor,

Thank you very much for all the thoughtful comments from you and the reviewers. We have revised the manuscript by using the red text according to your format and reviewer’s request.
If you have any further questions, please feel free to contact me. I am looking forward to hearing from you soon. Thank you very much for your considerations about our paper on the “BMC Anesthesiology”!

Sincerely,

Zhiying Feng

Jan 10, 2017

Please find the following Response to the comments of referees:

Abstract:

1. Several abbreviated terms are recommended to be modified or unified as follows: patient-controlled intravenous analgesia (PCIA) -> intravenous patient-controlled analgesia (IV-PCA), PCA -> patient-controlled analgesia (PCA).

Response:

I am so appreciated for your review and suggestion. We have revised the abbreviated terms according to your advice with IV-PCA in the whole paper with red one.

2. What is D/D ratio? Please, describe the full term.

Response:

Thank you for your good suggestion. The full term of D/D ratio is demand/delivery ratio.
3. "the hospital stay post-surgery" -> "the hospital stay after surgery"

Response:

Thank you for your kind advice. We carefully revised it according to your advice.

4. English editing is needed to clarify the meaning of some sentences.

Response:

Thank you for your good advice. We carefully revised it according to your advice.

Background:

1. Page 4, lines 76-77: Reference 2 is not relevant to this sentence because the reference was performed in the induction period and its focus was not postoperative pain. Thus, it should be replaced with a more proper reference

Response:

Thank you for your good advice. We carefully replaced references with following new references.


2. Page 4, line 84: Provide a reference which is relevant to this sentence.

Response:

Thank you for your good advice. We have added the references with following.


3. Page 4, line 90: after the procedure[5]. -> after the procedure [5].

Response:

Thank you for your good advice. We have revised it with after the procedure.
4. Page 4, line 90-92: Provide the references which is relevant to the sentence ("only a few studies have been conducted, ~").

Response:

Thank you for your good advice. We have add references as following:


5. Page 4, line 92: patient-controlled intravenous analgesia -> intravenous patient-controlled analgesia (IV-PCA)

Response:

Thank you for your good advice. We have revised according to your advice with IV-PCA in the whole paper.
6. Page 5, line 100: Reference 7 is about use of intrathecal hydromorphone. Please, replace it with one of intravenous hydromorphone.

Response:

Thank you for your kind suggestion. We have deleted ref 7 and added the following references:


7. Page 5, line 106: PCIA > IV-PCA (It should be identically modified in the whole remaining part of the paper.)

Response:

Thank you for your good advice. We have revised this abbreviated term with IV-PCA according to your advice.

8. Describe the hypothesis of the study in the end of the background.

Response:
Thank you for your good advice. We carefully described the hypothesis of the study with red one in the background.

we tested the hypothesis that hydromorphone could improve the postoperative mood for the patients with IV-PCA involved multimodal perioperative analgesia regimen compared to the sufentanil.

Materials and Methods:

1. In general, English editing including grammar or spacing is needed.

Response:

Thank you for your good advice. We carefully revised the manuscript editing including grammar or spacing.

2. Page 6, line 122: What does "abnormal operation or anesthesia" mean?

Response:

Thank you for your good advice. We carefully modified the sentence as following: a previous history of delay recovery under general anesthesia,....

3. Page 6, line 126: What does "15d" or "24h" mean?

Response:

Thank you for your good advice. “15d” means “15 days”. “24h” means “24 hours”. In order to express our meaning correctly, we carefully modified the sentence.

- taking monoamine oxidase inhibitor (MAOI) or antidepressant use 15 days before surgery, taking sedative, anti-emetic, or antipruritic during the 24 hours preoperatively,....
4. Page 6, lines 131-133: The sentence should be modified.

Response:
Thank you for your good advice. We carefully modified the Randomization section.

5. Page 7, lines 142-146: Please, simply present the scoring method or criteria of Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS).

Response:
Thank you for your good advice. We have added the scoring method of SAS and SDS.

- The SAS is a 20-item self-report assessment device built to measure anxiety levels, based on scoring in 4 groups of manifestations: cognitive, autonomic, motor and central nervous system symptoms. The SDS is a short self-administered survey to quantify the depressed status of a patient. There are 20 items on the scale that rate the affective, psychological and somatic symptoms associated with depression. Each question is scored on a scale of 1 through 4 (based on these replies: "a little of the time", "some of the time", "good part of the time", "most of the time"). Overall assessment is done by total score.

6. Page 9, line 196: What is PCA D/D ratio?

Response:
Thank you for your good suggestion. The full term of D/D ratio is demand/delivery ratio.

The aim of this investigation was to assess the impact of hydromorphone or sufentanil IV-PCA on mood and side effects and recovery for the patients undergoing radical surgery for colorectal cancer, pain was well controlled by IV-PCA. So, We have deleted D/D ratio in the revised version.
7. Page 11, line 234: Does "ANOVA" mean "one-way" or "two-way"? Also, "ANOVA" should be edited with "analysis of variance (ANOVA)". Describe it exactly.

Response:

Thank you for your good advice. We carefully described it based on your advice as following in the revised version:

- For continuous data, the overall differences were tested by one-way analysis of variance (ANOVA) followed…

8. Page 11, line 235: What is "LSD"?

Response:

Thank you for your good advice. The full name of "LSD" is least significant difference t-test.

9. Describe the infusion device and method of propofol.

Response:

Thank you for your good advice. We carefully described it based on your advice.

-- For anesthesia maintenance, propofol was titrated at 5–8 mg/kg/hour with pump to keep BIS between 45 and 55, and remifentanil was administrated at 0.05–0.3 g/kg/min with pump to keep haemodynamic stable.
10. The authors did not use a neuromuscular monitoring during surgery. How (and what) do you use a reversal agent for neuromuscular blockade? Please, describe it.

Response:

Thank you for your kind suggestion. Under the current State Health Insurance Policy in Mainland China, cost related to peripheral nerve stimulator is not reimbursable. Most patients refused to use nerve stimulator due to their willingness and capability for self-pay. According to Chinese Expert Consensus on Muscle Relaxant, the neuromuscular blockade is reversed with atropine and neostigmine when the train-of-four (TOF) count is 2 or spontaneous breathing occurs.

11. Describe the information of the PCA device.

Response:

Thank you for your nice advice. We have described the information of the PCA device in the paper.

PCA device - Rehn Medtech Ltd., Jiangsu, China

12. The study has too many outcomes and so it is very distracting. Simply summarize the primary and secondary endpoints.

Response:

Thank you for your nice advice. The primary and secondary endpoints were listed as following:

-- The primary endpoint was mood changes at 48h and 96h after surgery. The secondary endpoints were the incidence of opioid-related adverse effects and recovery results and patient satisfaction after surgery.
Results:

1. In general, English editing including grammar, spacing or reconstruction of some sentences is needed.

Response:

Thank you for your nice advice. We carefully revised it including grammar, spacing and reconstruction of lots of sentences.

2. Page 12, line 261 and Fig.4: What is PCA D/D ratio? Explain it.

Thank you for your good suggestion. The full term of D/D ratio is demand/delivery ratio. The aim of this investigation was to assess the impact of hydromorphone or sufentanil IV-PCA on mood and side effects and recovery for the patients undergoing radical surgery for colorectal cancer, pain was well controlled by IV-PCA. So, We have deleted D/D ratio in the revised version.

3. Table 6: Unlike the values of the title, "Postop.24h" and "Postop.48h" were falsely described in the table. Correct it.

Response:

Thank you for your nice advice. We have revised this table (now Table 5) with red one.
4. Table 7: Group H (n=37) -> Group H (n=35)

Response:
Thank you for your kind advice. The number of Group H was wrong by mistake. We have revised it with red one. (now Table 6)

5. Table 9: The sample size in each group was omitted.

Response:
The aim of this investigation was to assess the impact of hydromorphone or sufentanil IV-PCA on mood and side effects and recovery for the patients undergoing radical surgery for colorectal cancer, pain was well controlled by IV-PCA. So, We have deleted table 9 (Episodes of interrupting the IV-PCA because of other reasons.) in the revised version.

6. Table 10: The format of the table should be edited.

Response:
Thank you for your good advice. We carefully edited the format of this table. (now Table 8)

7. The results section is very distracting and difficult to understand. Reorganize the results with the order of the primary and secondary endpoints.
Response:

Thank you for your kind advice. We have reorganized the results with the order of the primary and secondary endpoints.

Discussion:

1. This section is too long at present. Please, reorganize the contents with the order of the primary and secondary endpoints.

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Response:

Thank you for your good suggestion. We have revised the discussion part according to your advice.

Please overwrite this text when adding your comments to the authors. This is a well-prepared comparative study. I have some suggestions:

Response:

I am so appreciated for your review and suggestion. We have overwrote this text based on your advice.

1. I am considering that the "score of anger" was your primary endpoint (I may be wrong, but I consider it according the sample size analysis)... Please give us a clear info about your primary endpoint, and inform in "results" first about your primary endpoint.
Response:

Thank you for your good advice. The primary endpoint was mood changes at 48h and 96h after surgery. The secondary endpoints were the incidence of opioid-related adverse effects, recovery results and patient satisfaction after surgery.

2. The first sentence of the "Discussion" needs to be corrected.

Response:

Thank you for your good suggestion. We have revised the discussion part according to your advice.

3. Do not give "doses" in Discussion.

Response:

Thank you for your good suggestion. We have revised the discussion part according to your advice.

4. Discussion is too long; focus on essential messages and "discuss" these message... Focus more on results that are "significant".

Response:

Thank you for your good suggestion. We have revised the discussion part according to your advice.
The authors conducted a clinical study on the effects of intravenous patient-controlled analgesia with Sufentanil compared to Hydromorphone after radical colorectal cancer surgery with emphasis on opioid related side effects, patient satisfaction scores and mood scores. The underlying idea of this study is original and to our knowledge there are only 2 other studies comparing sufentanil and hydromorphone in a randomized controlled setting (Saari et al. 2014 “Influence of intensive care treatment on the protein binding of sufentanil and hydromorphone during pain therapy in postoperative cardiac surgery patients” and Coda et al, 1997 “Comparative efficacy of patient-controlled administration of morphine, hydromorphone, or sufentanil for the treatment of oral mucositis pain following bone marrow transplantation”). These studies would need to be cited of course when discussing the results of this paper in the context of what has been found so far.

Response:

Thank you for your good suggestion. We have cited the above papers.

However, we do have major concerns regarding the planning and presentation of the study at hand and also regarding the way the manuscript is written (see below, p. 2-7).

1. We think that comparing sufentanil and hydromorphone in a postoperative patient-controlled setting is clinically relevant with the underlying aim to identify the optimal opioid that provides the best analgesia with the lowest incidence of adverse events. However, from our clinical experience based on an acute pain service that is run by our department for more than 20 years, changes in mood or patients getting angry from on opioid PCA is not a problem. In fact, it has never limited the therapy in any way and has never led to termination of this type of analgesia, nor has it influenced the choice of an opioid for PCA. In contrast, side effects like nausea and vomiting, pruritus, excessive sedation or respiratory depression are common and potentially dangerous and often limit the use of opioids. In the presented study, however, group sizes were calculated to identify changes in mood scores and this seems to be the primary endpoint, even though this is not stated in the paper. If this is the case, statements concerning other side effects become less important, since they result from multiple testing and would require a correction (i.e. Bonferroni), which was not performed. Assuming that changes in mood are the primary endpoint for this study (according to what the authors wrote regarding the sample size in the methods section), there needs to be some explanation, why it is clinically relevant. In other words, there needs to be a rationale to perform this study and the rationale must be clearly stated in the introduction and also needs to be addressed in the discussion. Accordingly, the authors need to demonstrate, how this study helps to resolve a clinically relevant problem.
Response:

Thank you for your good suggestion. According to your advice, we have stated and supplied the rationale to perform this study clearly in the introduction and in the discussion. We also added primary endpoint and secondary endpoint in the manuscript.

If this is the case, statements concerning other side effects become less important, since they result from multiple testing and would require a correction (i.e. Bonferroni), which was not performed.

Response:

Thank you for your kind suggestion. In our study, we compared the opioid-related adverse effects only between group S and group H at every point after surgery. Mood changes at T5 and T9 were compared with the preoperative measures in both groups respectively. And mood changes at T5 and T9 were also compared between group S and group H. Correction (i.e. Bonferroni) would not be required between two groups.

Accordingly, the authors need to demonstrate, how this study helps to resolve a clinically relevant problem.

Response:

Thank you for your good suggestion.

The ideal opioid would be one that provides rapid pain relief with moderate duration while at the same time producing minimal physiologic or psychologic side effects. Psychological processes directly influence clinical outcomes. Sufentanil and hydromorphone are opioid analgesics currently widely used in clinical anaesthesia and postoperative analgesia. Lots of literature paid much attention on their analgesia effect or physiological side effects, but less on their side effect on the psychologic issue. Stephan believed that the profound impacts of opioids on mood and wellness are often underscored.
2. Another concern is the way the authors dealt with the common confounders of opioid studies. These include an equal pain stimulus (or type of surgery in this case), in a patient collective that is free of other confounders like chronic pain (higher starting pain scores, pre-treatment with analgesics or increased tolerance) or history of drug abuse. The pain resulting from the stimulus is then treated with the interventions that are studied (in this case sufentanil/hydromorphone), while co-analgetics, antiemetics, etc. should be equally distributed among both intervention groups, so that the measures for the endpoints are not systematically altered. Accordingly, it is important not to look at pain scores only but also to consider the above mentioned confounders. These aspects need to be addressed in the discussion.

Response:

Thank you for your good suggestion.

-- To eliminate bias and increase comparability, we tried to keep the external conditions and procedures identical between the two groups, including type of surgery in this case. Other confounders like chronic pain (higher starting pain scores, pre-treatment with analgesics or increased tolerance) or history of drug abuse has been excluded. We have addressed these aspects in the discussion.

According to your kind advice, we have supply our standardized postoperative analgesic regimen for the patient in this investigation. Flurbiprofen axetil 50mg was injected 30 min before the end of surgery intravenously. At the end of surgery, the postoperative wound was infiltrated with 10 mL of 0.75% ropivacaine, then the IV-PCA pump was connected. The aim of postoperative analgesia was to control the VAS score below 3 after surgery. If the patient was not satisfied by two or three bolus doses administrated continuously by sufentanil PCA, flurbiprofen axeti 50 mg was administered for breakthrough pain by physicians on the ward. In the case of severe side effects, the IV-PCA was stopped. Then the acute pain service (APS) staff would reprogramming the pump with decreasing the basal dose and bolus dose by 20–25%. IV-PCA was reconnected after treating and severe side effects subsided. Antiemetics was routinely prophylactic use for every patient to prevent PONV.

3. Also, the presented pain scores in this review are too inaccurately presented to allow their further discussion and lack standard deviations. Although these difficulties when comparing opioids in a reliable way are not mentioned in the text, we do not see a critical methodological flaw in the study regarding this aspect. We also do not see any high risk of bias in this study and
it is to believe that the presented results resemble the differences between sufentanil and hydromorphone truly.

Response:

Thank you for your kind advice. We have revised the figure 2 to show the result of pain score.

Concerns related to various aspects which we found while going through the manuscript. The following includes a detailed list of comments about the abstract, background and methods section.

Abstract:

Background:

Information is only given about the aim of the study. This section misses information concerning the context of the study and the rationale for carrying out this study, i.e. what we already know and what needs to be studied.

Response:

Thank you for your good advice. We have stated information concerning the context of the study and the rationale for carrying out this study in the background based on your advice.

Methods:

This section lists many variables that were recorded:

VAS score at rest and during mobilization consumption of PCIA, PCA D/D ratio, and rescue analgesics perioperative moodside-effecthemodynamic changestime to recovery, drainage tube removal, walk, and the hospital stay post-surgery

However, it is not clear what the primary and secondary outcome measures were.
Thank you for your good advice. The primary outcome was mood changes at 48h and 96h after surgery. The secondary outcomes were the incidence of opioid-related adverse effects, recovery results and patient satisfaction after surgery.

- “PCA D/D ratio, … were recorded at various time points”

The abbreviation “PCA D/D ratio” is used without explaining what it means.

- Statistical tests used to analyze the data are not mentioned.

Thank you for your good suggestion. The full term of D/D ratio is demand/delivery ratio.

The aim of this investigation was to assess the impact of hydromorphone or sufentanil IV-PCA on mood and side effects and recovery for the patients undergoing radical surgery for colorectal cancer, pain was well controlled by IV-PCA. So, We have deleted D/D ratio in the revised version.

- “No significant differences between the groups were seen during the interruption of IV-PCA, patient satisfaction, time to gastrointestinal recovery …”

The abbreviation “IV PCA” is used without explaining what it means. Is it the same like “PCIA”? If that is the case why using a different abbreviation?

I am so appreciated for your review and suggestion. We carefully explained the meaning of the abbreviation “IV PCA”. And we modified “PCIA” into “IV- PCA”.

No significant differences were seen concerning what variables? Did you want to express that there were no differences concerning patient satisfaction, etc.

Variables that are not mentioned in the methods section should not be reported on in the results section (“patient satisfaction, the time to gastrointestinal recovery”).
Response:

I am so appreciated for your review and suggestion. We carefully revised it in the manuscript.

Conclusions:
- “could provide potent analgesia, satisfaction, and postoperative recovery for patients undergoing colorectal cancer radical surgery.”
- “satisfaction” was not mentioned in the methods section – why report on it in the conclusions?

Response:

Thank you for your good advice. We carefully revised the methods, results and conclusions based on your advice.

Conclusions:
- “could provide potent analgesia, satisfaction, and postoperative recovery for patients undergoing colorectal cancer radical surgery.”
- “satisfaction” was not mentioned in the methods section – why report on it in the conclusions?

- “satisfaction” needs to be changed to “patient satisfaction”

- “both … provide … potent analgesia” – as there was no significant difference concerning the potency of the opioids, why not mention it in this section? (e.g. “provide a similar level of (potent) analgesia)

- “both … provide … satisfaction” – what do the authors want to say? Both methods provide a similar level of patient satisfaction? Both methods provide a high level of patient satisfaction? – Please specify!

- “…but similar episodes of interrupting the IV-PCA due of nausea and vomiting.”
-“interruption of IV-PCA” is mentioned even though this variable has not been mentioned before (methods, results)

Response:
Thank you for your good advice. We carefully revised the conclusions based on your advice.

Trial registration:
- The date of registration is missing. Was the study registered prospectively or retrospectively?

Response:
Thank you for your good advice. We carefully added the date of registration.

“patient-controlled intravenous analgesia (PCIA)” instead of “analgesia” seems to be better; suggested key word (in addition): “side effects”

Response:
Thank you for your good advice. We carefully revised the keywords based on your advice.

C) Background

p.4, 70-72: The statement itself seems to be plausible. However, the reference cited [1, Lu et al. 2010] to support this statement cannot be found on PubMed. In addition, just from the title of the cited reference it is questionable that the cited reference is about “delayed recovery”, “postoperative depression” and “various clinical complications which may be life-threatening” as a consequence of unresolved postoperative pain.
p. 5, 80-81: “However, the evaluation of the anesthetic effects does not comprise only of the physiological index but also the psychological index [3].

It is not clear to the reviewers what the “physiological index” and “the psychological index” mean in the context of “the evaluation of the anesthetic effects”.

Moreover: “does not comprise only of ..” – meaning?

In addition: When submitting a manuscript to an international medical journal that has readers from all over the world it does not really make sense to cite an article [3, Jiang et al. 2009] that readers from other countries outside China don’t have access to!

p. 5, 87-88: The statement “In recent years, the mood alterations after anesthesia have become a topic of intensive scrutiny [4].” cannot be verified because the cited reference cannot be found either!!! Also, if there has been intense research going on in the past, the authors should be able to cite at least two papers.

p.5, 88-90: The authors report on an interesting finding. However, again (!!!), the statement cannot be verified because the reference cited cannot be found in PubMed!

Response:

Thank you for your kind suggestions. We carefully revised the background and cited new references which can be found in PubMed based on your advice.

p.5, 76-77: Also this statement (“Moreover, …) makes sense. However, the cited reference [2, Sun et al. 2011] does not support the statement at all because it simply reports on the effectiveness of dezosine to suppress fentanyl induced cough for induction of general anesthesia! A reference which would make sense in this context would report on a study that, for instance, demonstrates the positive effects of less side effects on patient satisfaction.
Response:

Thank you for your good advice. We carefully replaced these references with new references.

p. 5, 90-92: “Nevertheless, only a few studies have been conducted, hitherto, on the patterns of mood changes in patient-controlled intravenous analgesia.” Reference is missing.

Response:

Thank you for your good advice. We have provided the references for this sentence.

p. 5, 94-95: “Sufentanil, a highly selective opioid agonist…” the type of opioid receptors should be mentioned as the authors did for hydromorphone.

Response:

Thank you for your good advice. We carefully added the type of opioid receptor based on your advice.

p. 5, 100: Reference [7] can be deleted because it is an invited comment on an original research paper which reports on the intrathecal administration of hydromorphone vs. morphine by Lee et al. If, at all, the authors should have cited the paper by Lee et al. 2012.

Response:

Thank you for your kind advice. We carefully deleted the reference 7 and added new references.

p. 5, 103-106: The last sentence of this section enumerates the aims of the study including analgesic efficacy as the first aim (main outcome?) which is inconsistent with the title of the manuscript: “… impact on mood, opioid adverse effects and recovery.”
In addition, it is not clear, why all the study aims listed in this sentence are a consequence (“Therefore, …”) of the statements given in this section. In other words, the rationale for carrying out this study with these study aims is not at all presented convincingly:

- To date no comparison of hydromorphone vs. sufentanil concerning any variable that is mentioned (analgetic potency, etc.)?

- To date, no data concerning the effects of hydromorphone and sufentanil on the mood?

- Any reason for the comparison except for the fact that these two opioids are the ones used most commonly following this kind of surgery at the authors’ hospital?

Moreover: What is the hypothesis that was studied?

Response:

Thank you for your good advice. We revised this section based on your advice. Please see the part of background in detail.

D) Methods

Heading “study subjects” preceding the paragraph that describes the trial design etc. should be placed right above the corresponding paragraph. Accordingly, placement of many other headings should be reassessed!

Response:

Thank you for your good advice. We have revised according your suggestion.
Methodological aspects, Risk of Bias assessment

1) selection bias: low risk, computer generated randomization list, allocation concealment via sealed envelope (Improvements could be, who generated the list?, was it balanced block randomization?, who enrolled the patients? etc.)

Response:
Thank you for your good advice. We have revised it according to your suggestion in the relative part.

2) performance bias: (debatable) low risk, drugs prepared by uninvolved staff (nurse), all other staff is stated to have been blinded

Response:
Thank you for your good advice. The required number of subjects per group was determined as 33 when the α value (level of significance) was 0.05 (two-sided), and the power 1-β was 0.8. We further added an excess of 20% to the sample size in order to compensate for subject attrition, yielding a final group size of 80 patients. Finally, 72 patients completed the study. A total of 8 patients were excluded from the final analysis due to canceled surgery (2 patients), surgical procedure changed to per anum intersphincteric rectal dissection (3 patients), and liver resection because of tumor metastasis (3 patients).

3) attrition bias: low risk, incomplete outcome data 72/80 patients, dropouts explained

Response:
Thank you for your good advice. The aim of this prospective comparative investigation was to assess the impact of hydromorphone or sufentanil IV-PCA in a multimodal perioperative analgesic regimen on mood and side effects and recovery for the patients undergoing radical surgery for colorectal cancer based on similar analgesia effect. The primary endpoint was mood

4) reporting bias: low risk, all endpoints reported, no selective reporting

Response:
Thank you for your good advice. The aim of this prospective comparative investigation was to assess the impact of hydromorphone or sufentanil IV-PCA in a multimodal perioperative analgesic regimen on mood and side effects and recovery for the patients undergoing radical surgery for colorectal cancer based on similar analgesia effect. The primary endpoint was mood
changes at 48h and 96h after surgery. The secondary endpoints were the incidence of opioid-related adverse effects, recovery results and patient satisfaction after surgery.

From a conservative statistical point of view, the Kolmogorov-Smirnov-Test does not prove a normal distribution, although it is common practice to use it in this regard.

Response:
Thank you for your good advice. We have used the Shapiro-Wilk test to assess the normal distribution again based on your advice.

Elegibility criteria are not mentioned explicitly, they can only partially be guessed based on the patients that were actually enrolled.

p.7, 119: “.. 80 patients with American Society of Anesthesiologists (ASA) physical status I–II, aged 18–80 years, and scheduled for laparoscopic or open radical surgery for colorectal cancer were enrolled in the present study.”

How about ASA III patients? How about patients older than 80 years? Were they excluded or did they happen not to be enrolled?

Response:
Thank you for your kind advice. We have revised it according to your suggestion.

In addition: Number of patients assigned to the groups belongs into the results section.

Response:
Thank you for your kind advice. We have revised it according to your suggestion.

p. 7, 122: exclusion criterion: “abnormal operation or anesthesia” – please specify
Response:

Thank you for your good advice. We carefully modified the sentence.

- a previous history of delay recovery under general anesthesia, ...

p.8, 142-6: “…and Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) were …”.

These tests should be explained very briefly as most readers a very unlikely to be familiar with these tests. Accordingly, readers will not be able to understand why a score > 50 was chosen as a cut-off to exclude patients.

Response:

Thank you for your good advice. We have added the scoring method of SAS and SDS.

- The SAS is a 20-item self-report assessment device built to measure anxiety levels, based on scoring in 4 groups of manifestations: cognitive, autonomic, motor and central nervous system symptoms. The SDS is a short self-administered survey to quantify the depressed status of a patient. There are 20 items on the scale that rate the affective, psychological and somatic symptoms associated with depression. Each question is scored on a scale of 1 through 4 (based on these replies: "a little of the time", "some of the time", "good part of the time", "most of the time"). Overall assessment is done by total score.

p.9, 172 ff: The administration is described in a very confusing way: “Formula of PCA”, “Loading doses” using μg and later the authors just mention ml/h which makes it difficult for the reader to calculate how much of the drug patients get. The authors should give the concentration of the drugs in addition to ml/h.

Response:

Thank you for your good advice. We revised the administration of IV-PCA based on your advice.

- For group S, the pump was set to deliver with a loading dose of 3 g, a bolus dose of 3 g of sufentanil with a lockout time of 10 min with a continuous infusion at 1.8 μg/h, and a maximum dose of 18 g/h postoperatively. For group H, the pump was set to deliver with a loading dose of
0.25 mg, a bolus dose of 0.25 mg of hydromorphine with a lockout time of 10 min with a continuous infusion at 0.15 mg/h, and a maximum dose of 1.5 mg/h postoperatively.

p. 9, 182-3: “In the case … we interrupted the IV-PCA, adjusted its parameters, and …” – how were the parameters adjusted?

Response:
Thank you for your good advice. We revised the text based on your advice.

--If the patient was not satisfied by two or three bolus doses administered continuously by IV-PCA, flurbiprofen axetil 50 mg was administered for breakthrough pain by physicians on the ward. In the case of severe side effects, the IV-PCA was stopped. Then the acute pain service (APS) staff would reprogram the pump with decreasing the basal dose and bolus dose by 20–25%. IV-PCA was reconnected after treating and severe side effects subsided.

p. 10, 196: “PCA D/D” what does it stand for?

Response:
Thank you for your good suggestion. The full term of D/D ratio is demand/delivery ratio.

The aim of this investigation was to assess the impact of hydromorphone or sufentanil IV-PCA on mood and side effects and recovery for the patients undergoing radical surgery for colorectal cancer, pain was well controlled by IV-PCA. So, We have deleted D/D ratio in the revised version.

p. 11, 223: “… in order to estimate the size of the group essential for the main study.” Apparently, the authors want to express that anger is the primary outcome variable. Accordingly, they should have mentioned this above in a separate section called “primary and secondary outcome measures”.

Response:
Thank you for your good advice. We have add the primary and secondary outcome measures.
E) Results

The D/D ratio graph and the pain score graphs not to be revised. The pain score graph is arguably the most important and the first graph to look at, when reading the paper and an indicator for equianalgetic dosing of the opioids and therefore reliable scores and event rates among the groups. It needs to be more precise, at least to decimals, and contain the standard deviations.

Response:

Thank you for your kind advice. We have revised the figure to show the result of pain score.

The aim of this investigation was to assess the impact of hydromorphone or sufentanil IV-PCA on mood and side effects and recovery for the patients undergoing radical surgery for colorectal cancer, pain was well controlled by IV-PCA. So, We have deleted D/D ratio in the revised version.

F) Discussion

Despite the concerns mentioned in the beginning, a minor comment would be the discussion of the lipophilicity and the blood brain barrier regarding the area postrema and the circumventricular organ. Since there are no tight junctions in this area of the brain, lipophilicity is not of importance to cause nausea and vomiting here, yet lipophilicity may play a role in transmitter (serotonin, dopamine) related nausea and vomiting or “postoperative nausea and vomiting” (PONV), which is not primarily depending on the opioid used, but rather multifactorial and depending on the anesthesia and risk factors of a patient, but another aspect that could be discussed.

Response:

Thank you for your kind advice. We have revised it in the discussion.
Grammar / Spelling Mistakes:

Minor aspects related to spelling, grammar and style (the following list includes just a few examples of the many mistakes than can be found all over the manuscript):

“the anger scores in the hydromorphone group were significantly low (P<0.05), but the incidences of pruritus and nausea were high (P<0.05).”

This should be corrected to … were significantly lower …. were higher

“ … were seen during the interruption of IV-PCA”

Response:

Thank you for your good advice. We carefully revised it based on your advice.

- Compared with group S, the anger scores in the group H at 48h and 96h after surgery were significantly lower (P =0.012 and 0.005, respectively), but the incidences of pruritus and nausea were higher (P =0.028, 0.008 respectively).

I assume the authors refer to the period following termination of PCIA. Therefore, it would make sense to rephrase it as follows:“were seen in the period following termination of …”

Response:

Thank you for your good advice. We carefully revised the manuscript and deleted this sentence.

“ …could provide potent analgesia,…”

Why use the word “could” in this context? It can be deleted. Rephrase as follows: “… provided potent analgesia”
Response:
Thank you for your good advice. We carefully revised the manuscript and deleted this sentence.

“… for patients undergoing colorectal cancer radical surgery.”
Please rephrase as follows: “… undergoing radical surgery for colorectal cancer.”

Response:
Thank you for your good advice. We carefully revised the manuscript based on your advice.

“…but similar episodes of interrupting the IV-PCA due of nausea and vomiting.” Please rephrase as follows: “due to nausea and vomiting.”

Background

Response:
Thank you for your good advice. We carefully revised the manuscript and deleted this sentence.

Background

5 – 79 the patients’ demands of medical comfort have also elevated, especially in the case of anesthetic effects.

Response
Thank you for your good advice. We carefully revised the background.

p. 5, 81-82 “The postoperative pain results in …” should be corrected to “Postoperative pain results in …”
Response:
Thank you for your good advice. We carefully revised the manuscript based on your advice.

6 – 97 and has been widely used as an intravenous analgesia in China [6]

Response:
Thank you for your good advice. We carefully revised the manuscript based on your advice.

Methods
Mix of BE and AE: p. 8, 147-150: “pre-anesthetic” and “induction of anaesthesia”

Response:
Thank you for your good advice. We carefully revised the manuscript based on your advice.

p.8, 149: “pulseoximetry” should be corrected to “pulse oximetry”

Response:
Thank you for your good advice. We carefully revised the manuscript based on your advice.

p.9, 180: “twice or thrice” …three times!

Response:
Thank you for your good advice. We carefully revised the manuscript.