Author’s response to reviews

Title: Comparison of ropivacaine combined with sufentanil for epidural anesthesia and spinalepidural anesthesia in labor analgesia

Authors:

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Author’s response to reviews:

Reviewer reports:

Antonio Ragusa (Reviewer 1): In this study, the authors have compared retrospectively the use and effectiveness of two anaesthetic techniques: continuous epidural anesthesia (CEA) and combined spinal-epidural anesthesia (CSEA), using the ropivacaine (a local anesthetic) combined with the sufentanil (an opioid) in primiparous women at term pregnancy. Results indicate that the use of the two drugs with the combined technique CSEA can reduce the times of labor with an improved maternal satisfaction.

For the specific aim of this study, a continuous background infusion via pump with additional dose controlled by the patient (patient-controlled analgesia (PCA)) was chosen.

In the recent literature, no scientific articles that compare the two techniques of anesthesia in labor using the two drugs disclosed (ropivacaine combined with sufentanil) and with the technique of patient-controlled analgesia (PCA) were found.

There is a Cochrane Review from 2018 (not cited in the bibliography of this article) which compares epidural versus non-epidural or epidural versus no analgesia in labor, and found out that epidurals may reduce pain during labor more effectively than any other form of pain relief.

The main limitation of this study is its retrospective design. Hence, additional prospective and adequately powered studies are needed to confirm findings and determine the optimal combination of volume, rate, time, and drug concentration.

Reply: Thanks for your careful and professional review. Large randomized controlled study is our goal in the near future, to confirm our findings in this study and determine the optimal combination of volume, rate, time, and drug concentration, therefore providing guidance for the gynecologists and obstetricians during their clinical practice.

Moreover, in this study only primiparous women were included. Further research should be conducted on this topic including multiparous women.

Reply: Thanks for your careful and professional review. We will consider including multiparous women in our future research to reinforce our findings.

Interestingly, the authors have also evaluated some adverse drug reaction in two groups of patients. It would have been interesting to evaluate other drugs collateral effects such as headache, fever, shivering and hypotension. However, the small amount of cases doesn't allow such evaluation.

Reply: Thanks for your careful and professional review. For the evaluation of other drugs collateral effects such as headache, fever, shivering and hypotension, large randomized controlled study is needed.
and we will include these collateral effects of drugs in our future research, to deeply investigate the findings in this study.

Reviewer 2 (Reviewer 2): "PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?
Yes - there is a clear objective
Reply: Thanks for your careful and professional review.

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
No - there are minor issues
Reply: Thanks for your careful and professional review. We had made some revisions and please check it in the revised manuscript.

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?
Yes - experiments and analyses were performed appropriately
Reply: Thanks for your careful and professional review.

STATISTICS - Is the use of statistics in the manuscript appropriate?
No - there are issues with the statistics in the study
Reply: Thanks for your careful and professional review. We had made some revisions in section “Statistical Analysis” and please check it in the revised manuscript.

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
Yes - the author's interpretation is reasonable
Reply: Thanks for your careful and professional review.

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?
Probably - with minor revisions
Reply: Thanks for your careful and professional review. We had made some revisions and please check it in the revised manuscript.

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: The authors have clearly mentioned the objectives, executed and interpreted their findings but have not clearly mentioned the study design. They have compared two modalities of ropivacaine combined with sufentanil for continuous epidural anesthesia (CEA) and combined spinal-epidural anesthesia (CSEA) in labor analgesia in terms of onset time and labor period, analgesic effect, adverse drug reactions rates and subject satisfaction perspectives and found that the CSEA modality would be superior to the CEA modality. This might be guidance for the gynecologists and obstetricians during their clinical practice but with necessary verification due to various limitations of the study including retrospective study, single-centric study, small sample size and other.
Reply: Thanks for your careful and professional review. Large randomized controlled study is our goal in the near future, to confirm our findings in this study and determine the optimal combination of volume, rate, time, and drug concentration, therefore providing guidance for the gynecologists and obstetricians during their clinical practice.
The authors have analyzed their data applying Student's t test, \( \chi^2 \) test and repeated measure ANOVA and interpreted the findings in tabular forms to make the findings trustworthy. They have clearly interpreted other findings with descriptive statistics (mean±SD) as well.

The authors have not specifically mentioned the conditions for the applications of the various statistical tests. They have also not mentioned the statement about normality checking of their dataset with P-P plot or Q-Q plot to confirm that the application of Student's t test and repeated measure ANOVA tests. If data were not normally distributed, you would have to apply Friedman's test (not repeated measure ANOVA) and Mann-Whitney U test (not independent t test). Other comments have been provided with this peer review.

Reply: Thanks for your careful and professional review. Section “Statistical Analysis” has been revised to “All statistical analyses were conducted with SPSS software, version 18.0 (SPSS Inc, Chicago, USA). PP plot (probability-probability plot) indicates the normal distribution of data. Values are presented as mean ± standard deviation (SD) or number (percentage) at appropriate. Quantitative variables (VAS scores, labor time, apgar scores and doses of ropivacaine and sufentanil) were compared by Student’s t test and \( \chi^2 \) test was used for categorical variables (adverse pregnancy outcomes and adverse drug reactions). Repeated-measures ANOVA were used for the comparison of different time points within the group. All reported P values are two-sided, and P value of less than 0.05 was considered statistically significant.”, please check it in the revised manuscript.

ADDITIONAL REQUESTS/SUGGESTIONS:

General comments:
* Use past tense in Methods and limitations sections.
Reply: Thanks for your careful and professional review. We have corrected some grammatical mistakes in Methods and limitations sections, please check it in the revised manuscript.

Specific comments:
Methods:
* Mention study design specifically; from the statement it seems that it was case-control study. Clarify this.
Reply: Thanks for your careful and professional review. The study design “In this retrospective, single-center case-control analysis” has been added to section “Study design and population”, please check it in the revised manuscript.

* Mention the basis of sample size calculation in both continuous epidural anesthesia (CEA) and combined spinal-epidural anesthesia (CSEA) groups. If this was case-control study, control: case ratio should be either 1:1 or 2:1 or 3:1 or 4:1. Clarify the issue.
Reply: Thanks for your careful and professional review. As a retrospective case-control analysis, control: case were 1:1. We have added this sentence to section “Study design and population”, please check it in the revised manuscript.

Study population:
* You've mentioned "All subjects were American Society of Anesthesiologists (ASA) … CEA group were class I." Sample size seems contradictory to that mentioned in the first sentence of this section i.e., "A total of 360 cases of voluntary … selected in this study retrospectively" and also contradictory to those mentioned in tables 1-7. Clarify the concern.
Reply: Thanks for your careful and professional review. We included 360 cases in the study and were divided into CSEA group and CEA group (n=180 in each group). Among which 142 subjects in CSEA group and 133 subjects in CEA group were class I and 18 subjects in CSEA group and 27 subjects in CEA group were class II. We have revised section “Study population” to make it clear, please check it
in the revised manuscript.

Statistical Analysis:
* Specify the exact conditions for the applications of those statistical tests mentioned in the sentence "Quantitative variables were compared by Student's t test and $\chi^2$ test was used for categorical variables."
Reply: Thanks for your careful and professional review. The sentence “Quantitative variables (VAS scores, labor time, apgar scores and doses of ropivacaine and sufentanil) were compared by Student’s t test and $\chi^2$ test was used for categorical variables (adverse pregnancy outcomes and adverse drug reactions).” has been added to section “Statistical Analysis”, please check it in the revised manuscript.

* You've mentioned "Repeated-measures analysis of variance were used for the comparison of different time points within the group." Did you check normality distribution of data with P-P plot or Q-Q plot? If so, mention those statements. If data were not normally distributed, you would have to apply Friedman's test. Clarify the issue.
Reply: Thanks for your careful and professional review. The statement “PP plot (probability-probability plot) indicates the normal distribution of data.” has been added to section “Statistical Analysis”, please check it in the revised manuscript.

Discussion:
* You've mentioned "The limitation of this study is that … epidural anesthesia were not suitable for this method." If you collected data retrospectively, your role was just to retrieve data from the file or repository or database. So, justify how technical expertise was required for this purpose if this was not prospective study?
Reply: Thanks for your careful and professional review. There were indeed an unclear translation during the process of our translator and the sentence has been revised to “The limitation of this study was that pregnant women with contraindication to epidural anesthesia were not suitable for this method.”, please check it in the revised manuscript.

References:
* References 1-8, 11, 13-24: Either mention 'doi' before digital object identifiers or skip these when you've mentioned year of publication, volume and/or issue and page number to save the space of the journal.
Reply: Thanks for your careful and professional review. The references has been updated and ‘doi’ has been deleted, please check it in the revised manuscript.