Author’s response to reviews

Title: Continuous intravenous infusion of remifentanil improves the experience of parturient undergoing repeated cesarean section under epidural anesthesia, a prospective, randomized study

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Version: 2 Date: 19 Nov 2019

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Reviewer reports:
Ohashi Yayoi (Reviewer 3): Interesting article regarding the use of remifentanil to reduce the visceral pain at repeat elective cesarean section (CS) under epidural anesthesia alone.
My institution rarely gives an epidural anaesthesia alone for elective CS (except special high risk cases), uses spinal anesthesia or CSE. If the adequate dose for spinal anesthesia (with opioids) was used, we hardly experience visceral pain during the surgical period even on the repeat CS. However I understand that visceral pain can occur during CS under spinal alone as well as epidural anesthesia. Therefore this study has a content to read.
Response: Thank you for your positive suggestions.
Firstly the weakness of this study was no blindness. I understand that you added "not designed to be a double-blinded study" for APGAR score in your discussion. A previous study with dexmedetomidine compared the dexmedetomidine effect with placebo (NS). In your study, it is hard to exclude the patients' perception (receiving IV pain killer/sedatives) and this bias should be discussed/stated in the manuscript.
Response: Thank you for your suggestions. We have revised it in our manuscript. See page 9-10.
“......and it was hard to exclude the patients' perception, which would increase the bias.”

If the analgesia is adequate for the procedure, it must difficult for patients to describe pain or discomfort. Was the VAS measured for sharp pain or did you include dull pain or any sorts of pain ?
Response: In our study, the VAS scores included any sorts of pain. We are sorry for the obscure writing.

The use of remifentanil in pregnancy is outside of the product licence/off label. Please state it in the manuscript.
Response: Indeed, the use of remifentanil in pregnancy is off label. Thus, we state it in our manuscript.
Thanks. “Many studies have shown that remifentanil (an off label drug for parturient) has less adverse
neonatal or maternal effects during cesarean section”. See page 3.

P3 Background "epidural anesthesia "is not" (I would suggest you to change to "must not be") a pleasant experience."
Response: Thanks, we have revised it. “Additionally, when the anxiety regarding surgery is included, epidural anesthesia must not be a pleasant experience for parturients.” See page 3.

P3 "remifentanil has almost no adverse neonatal or maternal effects" --- this statement is not true. You may or may not be aware that serious adverse effects (respiratory depression, bradycardia, cardiac arrest etc) with remifentanil (IVPCA for labour analgesia) to neonates and mothers/pregnant women have been reported in the past. Although you may want to argue the difference in remifentanil administration during between labour analgesia and CS, I still believe that its' worth emphasising the greater caution of using remifentanil as sedatives/anaesthetics in Obstetric anaesthesia.
Response: Thank you for your suggestions. In our revised manuscript, we have revised it. “Many studies have shown that remifentanil (an off label drug for parturient) has less adverse neonatal or maternal effects during cesarean section”. See page 3.

P4 Method, Did you monitor the end tidal CO2 (EtCO2) during the remifentanil administration? Severe respiratory depression with IV remifentanil has been reported and the use of EtCO2 monitoring is recommended. SpO2 cannot detect the early stage of respiratory depression. If EtCO2 was not used, please state the reason why.
Response: Thanks. In our routine practice, Carbon Dioxide sampling catheter was always used to monitor the respiratory rate and EtCO2. It can provide an accurate respiratory rate, but the value of EtCO2 was not accurate. Thus we did not describe it in detail in our manuscript because of the inexact EtCO2.

Also you measured RR, how did you measure RR continuously?
Response: In our study, Carbon Dioxide sampling catheter was used to monitor the respiratory rate and EtCO2. Thanks.

P5 How quickly did you allow to increase the remifentanil infusion rate?
Response: We have revised the manuscript based on your advice. See page 5. “The intravenous infusion rate of remifentanil was increased by 0.025 μg·kg⁻¹·min⁻¹ if patients complained of discomfort or pain, and the next rate of 0.025 μg·kg⁻¹·min⁻¹ would increase if the discomfort or pain was not relieved after 5 min.”
P5 Please state more details (dose, bolus/continuous infusion, frequency) of Ketamine administration.
Response: We have revised it in our manuscript. See page 5. “Intravenous infusion of ketamine was administered as required (0.5 mg/kg per dose, repeated for 20 min if necessary) or general anesthesia was performed in both groups if the discomfort or pain were not relieved.”

P5 What is "pressure mask"?
Response: We are sorry for the obscure writing. We have revised the sentence as following. “If the saturation of pulse oxygen (SpO2) was<95% or respiratory rate (RR) was<8 times/min (i.e., respiratory depression was observed), the parturient was awakened, and assisted breathing was applied.”

P7 Result, What is your consideration regarding the reason why the Ketamine administration did NOT differ between the two groups despite the VAS was significantly lower in Group R?
Response: In China, the use of ketamine in obstetric anesthesia was more prudent. Generally, the maternal opinion will be sought when the ketamine was administrated. If the maternal thought that the
pain could be tolerated, and ketamine would generally not be added for the time being. In our study, the VAS scores of maternal in group E were mainly distributed at 3 to 4 points. Thus, the number of parturients with additional ketamine was relatively small. Therefore, although there were differences in pain levels between the two groups, there was no difference in the use of ketamine.

P8 Discussion, please site the references that you used for "In the current study, approximately 67.5% parturients experienced pain"--- if this (current study) means your this study, please state what the definition of "pain" was. Is it VAS more than 4?
Response: Thanks for your suggestions. We have revised it in our manuscript. See page 8. “In the current study, approximately 65.8% parturients experienced pain (VAS scores≥4)during surgery without remifentanil, which was an apparent increase compared with the rate in previous studies[4,13] because the subjects were undergoing repeated cesarean section. “

P8 "...........which was an apparent increase compare with the rate in previous studies" -- please site the references for "previous studies".
Response: Thank you. We have site the references for "previous studies". See page 8. In the current study, approximately 65.8% parturients experienced pain (VAS scores≥4) during surgery without remifentanil, which was an apparent increase compared with the rate in previous studies[4,13] because the subjects were undergoing repeated cesarean section.

P8 You quoted the reference 14 for the statement "even if the sensory block plane reaches T4, many maternal complaints remain regarding unpleasant feeling related to visceral traction". As far as I did read and understood the reference 14, there is no single statement of "visceral traction", rather the author stated that the intervention was required due to anxiety, loss of sensation etc. Please find a better reference which suits your statement.
In the seventh edition of Miller’s Anesthesia, the description was also found.

Thanks for giving me this opportunity to review your manuscript. All the best on your submission.
Response: Thank you very much.