Author's response to reviews

Title: Comparison of intraoperative blood loss during spinal surgery using either remifentanil or fentanyl as an adjuvant to general anesthesia

Authors:

Hiroaki Kawano (hir.kawano@gmail.com)
Sawa Manabe (sawa0811@hotmail.com)
Tomomi Matsumoto (tomomo017@yahoo.co.jp)
Eisuke Hamaguchi (ehamaguchi0921@yahoo.co.jp)
Michiko Kinoshi (mt158@mac.com)
Fumihiko Tada (shunaihei@gmail.com)
Shuzo Oshita (shuzo@clin.med.tokushima-u.ac.jp)

Version: 2 Date: 11 October 2013

Author's response to reviews: see over
October 11, 2013

Dr. Thomas A Rowles  
Executive Editor, *BioMed Central Anesthesiology*

Dear Dr. Rowles:

We would like the revised manuscript titled “Comparison of intraoperative blood loss during spinal surgery using either remifentanil or fentanyl as an adjuvant to general anesthesia” considered for publication as an Original Research Article in *BioMed Central Anesthesiology*.

We are most grateful to you and the reviewers for the helpful comments on the previous version of our manuscript. We have taken all of these comments into account and re-submitting a revised version of our manuscript.

As can be seen by our specific responses to the reviewers, we have addressed all of the reviewers’ concerns in the revised manuscript, and we hope that our explanation and revisions are satisfactory.

We hope that the revised version of our paper is now suitable for publication in *BioMed Central Anesthesiology* and we look forward to hearing from you at your earliest convenience. Thank you for your time and effort in considering our revised manuscript for publication in *BioMed Central Anesthesiology*.

This manuscript has not been published and is not under consideration for publication elsewhere. All authors have read the manuscript and have approved this submission. The authors report no conflicts of interest. The manuscript has been carefully reviewed by an experienced English-language science editor.

Sincerely,

Hiroaki Kawano, M.D., Ph.D.  
Department of Anesthesiology, Tokushima Prefectural Central Hospital, 1-10-3 Kuramoto, Tokushima 770-8539, Japan  
Tel: +81-88-631-7151; Fax: +81-88-631-8354; E-mail: hir.kawano@gmail.com
We thank the reviewers for their thoughtful comments and criticisms.

Editorial comments

We would ask you to include the full name of the ethics committee that approved your study in this statement.

Response: According to your suggestion, we have reworded this part to “The study was approved by the Ethics Committee of National Hospital Organization Zentsuji Hospital” in our revised manuscript.

(Page 8, Lines 2)
This retrospective study compares intraoperative blood loss during spinal surgery in patients administered either remifentanil or fentanyl as an opioid adjuvant during general anesthesia for spinal surgery. In addition to intraoperative blood loss, indices of hemodynamic stability, including heart rate and systolic, mean, and diastolic blood pressure were compared over the entire perioperative period.

Intraoperative blood loss was lower in the remifentanil group and this group exhibited significantly lower intraoperative arterial BP than the fentanyl group.

Patient selection was well suited as patients who received induced hypotensive anesthesia were excluded: the AA selected two well matched series of patients and administered intraoperative remi or fentanyl as an opioid adjuvant.

Hemodynamic parameters were recorded at several points: before induction of anesthesia; at skin incision; 30, 60 and 90 min after skin incision; and at the end of anesthesia. Laboratory levels of preoperative and postoperative hemoglobin, hematocrit, and platelet count were also obtained and these data confirm well the results displayed. The infusion rate of remifentanil or the dose of fentanyl during maintenance was left to the discretion of the attending anesthesiologist. The primary end point was the estimated intraoperative blood loss, which was calculated from surgical suction volume and the weight of the gauze from the operative field.

There were no significant differences in the demographic variables age, gender ratio, weight, height, body mass index, ASA physical status, and history of hypertension between anesthetic groups (Table 1).

Similarly, there were not significant differences in the intraoperative variables duration of anesthesia, operation time, site of surgery (cervical vs. lumbar spine), or number of decompression segments.

Intraoperative SBP, MBP, and DBP were lower in the remifentanil group at all intraoperative measurement times (P < 0.05 for all hemodynamic parameters), suggesting that remifentanil may decrease intraoperative blood loss by inducing a sustained drop in BP during the intraoperative period.

Postoperative Hb and Hct values were in fact significantly reduced only in the Fentanyl group of patients.

In addition, more ephedrine was used in the remifentanil group than in the fentanyl group, and more nicardipine was used in the fentanyl group than in the remifentanil group, indicating that continuous infusion of remifentanil cause a greater suppression of the endocrine stress and inflammatory responses than intermittent boluses of fentanyl.
Although intraoperative hemodynamic stability can be achieved by administration of relatively large doses of any anesthetic agent, such treatment may delay extubation or recovery, particularly the time until patients can respond to queries posed by the clinicians. Furthermore, delayed awakening from anesthesia may complicate postoperative neurological assessment after spinal surgery. Times to patient response post-op is crucial and remifentanil provides a useful alternative management.

This paper is acceptable and well done.

**Response:** We thank the reviewer for the thoughtful comments.
1. First, the authors haven’t shown the readers the great interest level about this topic because it was a well-known fact. The results of this study can’t offer too much information to the readers.

Response: As you pointed out, several previous studies have reported that remifentanil provided better intraoperative stability than other opioids (i.e., fentanyl, alfentanil, or sufentanil) used during general anesthesia.

(Page 12, Lines 6-14)

However, these previous studies focused on hemodynamic changes associated with surgical stress rather than on the effects of different opioids on intraoperative bleeding.

(Page 13, Lines 4-5)

Furthermore, it has been demonstrated that the amount of bleeding during surgery is strongly dependent on arterial BP. Induced hypotension has long been used as an effective method for decreasing intraoperative blood loss during spinal surgery. In contrast to induced hypotension using volatile anesthetics, the effect of the intraoperative administration of opioid analgesics on blood loss was not previously examined.

(Page 14, Lines 3-10)

In this study, we demonstrated that administration of remifentanil during general anesthesia significantly decreased intraoperative blood loss compared with that of fentanyl. This is the first study to show that the selection of adjuvant opioid analgesic significantly influences intraoperative blood loss during spinal surgery.

(Page 12, Lines 2-5)

2. Second, the results were not so reliable not only because it was retrospective but also there were some other major confounding factors (for example, different surgeons and anesthetic depth) related to the endpoints.
**Response:** According to your suggestion, we have added a sentence “All operations were performed by the same surgeon.” in our revised manuscript.

(Page 8, Line 7)

As you pointed out, the bispectral index was not available as indicator of the level of consciousness during general anesthesia; therefore, decreased blood loss may have depended, at least in part, on differences in the dose of sevoflurane. However, it has been shown that sevoflurane dosage was significantly lower in patients who received remifentanil as an opioid adjuvant to general anesthesia instead of fentanyl. Therefore, we propose that the enhanced intraoperative hemodynamic stability observed in the present study was because of administration of remifentanil.

(Page 15, Lines 7-13)

3. Third, the criteria of using ephedrine or nicardipine was not clearly mentioned.

**Response:** Because of retrospective study design, the criteria of using ephedrine or nicardipine was left to the discretion of the attending anesthesiologist. Therefore, as you pointed out, the difference in amount of ephedrine or nicardipine may not be so reliable to show that remifentanil stabilizes intraoperative hemodynamics. We therefore compared indices of intraoperative hemodynamic stability including heart rate and blood pressure, and demonstrated that the remifentanil group exhibited significantly lower intraoperative arterial blood pressure than the fentanyl group.

(Figure 1)

4. Results: In Table 2, total fentanyl dose was significantly greater in fentanyl group than in the remifentanil group. It is not reasonable and meaningful to compare the dosage of intraoperative fentanyl (Fentanyl group) with postoperative fentanyl (Remifentanil group). Of course it would be significantly different.
**Response:** Table 2 shows the difference in the dose of intraoperative fentanyl between groups. In the fentanyl group, the patients were given a total of 272 ± 79 µg of fentanyl during surgery. In the remifentanil group, the patients received 112 ± 74 µg of fentanyl for transitional analgesia. No patients in both groups received fentanyl postoperatively.

(Table 2)

We have reworded this part to “Total dose of intraoperative fentanyl was significantly greater in the fentanyl group than in the remifentanil group” in our revised manuscript.

(Page 10, Lines 11-12)

We have also reworded to “In the remifentanil group, remifentanil was administered by continuous infusion for intraoperative analgesia, and fentanyl was administered for transitional analgesia.” in our revised manuscript.

(Page 9, Lines 1-3)

5. Results: In Table 3, the blood loss was significantly lower in remifentanil group. However, postoperative Hgb and Hct levels were lower in the remifentanil group. The blood loss was not compatible with the Hgb and Hct.

**Response:** For the analysis of intraoperative blood loss, laboratory levels of postoperative hemoglobin, hematocrit, and platelet count should ideally be measured just after the surgery. In our patients, however, the time point of blood sampling was irregular. These values may thus reflect both intraoperative and postoperative blood loss. We have added this limitation with retrospective study in our revised manuscript.

(Page 17, Lines 4-7)

Response: According to your suggestion, we have corrected.

(Page 13, Line 13)

7. Table 4 is suggested to be changed into Fig.1.

Response: According to your suggestion, we have changed table 4 to figure 1.

(Figure 1, Page 19, “Figure Legends” section)