Author’s response to reviews

Title: Observations on significant hemodynamic changes caused by high concentration of epidurally administered ropivacaine: Correlation and prediction study of stroke volume variation and central venous pressure in thoracic epidural anesthesia

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Version: 1 Date: 15 Jul 2017

Author’s response to reviews:

Responses to reviewer’s comments
First of all, we really appreciated with your scrupulous comments to our study. We revised our manuscript extensively as your comment. Although our manuscript was revised from authorized translator, there would be some odd expressions because of problem in our linguistic quality. Please consider generously following answers to your comments.

Reviewer 1)

1. Please correct the title for there is significant blood pressure change, SVR changes only in the groups with 60mg bupivacaine.
   
   A) As your comment, we corrected the title. Thank you for good comment.

Revised title is following:

Page 1
Observations on significant hemodynamic changes caused by high concentration of epidurally administered ropivacaine: Correlation and prediction study of stroke volume variation and central venous pressure in thoracic epidural anesthesia

2. Conclusion: as the authors controlled the volume injected into epidural space, the dose is dependent on concentration of bupivacaine. I think the authors are suggesting that there is higher risk of hypotension while using 0.75% bupivacaine epidurally. Higher dose means that with a large volume in low concentration (the same dose) may cause the same effects. However, that can not be concluded in this investigation.

A) Thank you for your helpful comment. We have changed direction by comparing hemodynamic data according to concentration difference and we revised all the manuscript following your comment.

Revised manuscript is following:


Methods: One hundred and twenty patients were randomly divided into three groups to epidurally receive 8 ml of 0.75%, 0.375%, or 0.2% of ropivacaine. Hemodynamics were monitored for 30 min after loading. We analyzed hemodynamic changes in subgroups according to age at 60. Receiver operating characteristic (ROC) analysis was performed to characterize the relationship between SVV, CVP and 20% decrease in mean arterial pressure (MAP) following TEA.

Results: MAP and systemic vascular resistance index were decreased and SVV was increased in 0.75% ropivacaine group. In 0.75% group, there was a significant difference in hemodynamics depends on the age but not in the other groups. SVV showed negative correlation with MAP whereas CVP showed no correlation. ROC analysis of SVV demonstrated weak predictive ability for 20% decrease in MAP at 10 min after loading dose with area under the curve of 0.687 with 9.5% of optimal cut-off value (sensitivity of 60.6% and a specificity of 68.9%).

Conclusions: High concentrations of ropivacaine caused severe hypotension and SVV changes, and these changes were more severe in the aged patients. SVV has a limited ability to predict hypotension following TEA, although SVV showed better correlation with hemodynamics than CVP.

Page 4. Introduction

In current study, we tested the hypothesis that hemodynamic derangement following epidural anesthesia is more significant on higher concentration of LA, administered in patients undergoing major upper abdominal surgery.

Page 6. Methods

Patients
One hundred and twenty patients scheduled for major abdominal surgery under TEA combined general anesthesia were randomized in a double-blinded method to receive one of three different concentration study solutions in 8 ml of volume after the induction of anesthesia: 0.75% ropivacaine (60 mg), 0.375% ropivacaine (30 mg), or 0.2% ropivacaine (16 mg).

Page 10. Results

Two from 0.75% ropivacaine group, 6 from 0.375% ropivacaine group and 3 from 0.2% ropivacaine group were excluded (Fig. 1). No statistically significant differences were seen among the groups regarding to age, sex, height, weight, ASA PS, fasting time, mean fluid administration until the end of the study, and type of surgery (Table 1).

In the aspect of concentration effect, MAP (P = 0.039) and SVRI (P = 0.026) were significantly decreased in 0.75% ropivacaine group compared with other groups. Concordant increase in SVV was remarkably increased in 0.75% group compared with 0.375% and 0.2% ropivacaine group through the study period (P=0.017).

Moreover, the proportion of patients who needed ephedrine was remarkably higher in 0.75% ropivacaine group (p = 0.04, Table 1).

Through the observation period in the same group, MAP (P < 0.001), SVRI (P = 0.009), and CI (P = 0.001) showed significant changes following time and lowest value at T10, whereas SVV (P = 0.031) showed distinct change, but the highest value at T10 compared with baseline value in 0.75% ropivacaine group. CVP (P = 0.012) and SVI (P = 0.309) showed no significant changes among the time points in 0.75% ropivacaine group. In contrast, these changes were not apparent in 0.375% and 0.2% ropivacaine group. Although there were significant changes in MAP (P < 0.001 in 0.375% and 0.2% ropivacaine group) and HR (P < 0.001 in 0.375% and 0.2% ropivacaine group) depend on time points, other hemodynamic parameters did not show significant changes following time (Fig. 2).

Hemodynamic data measured in two subgroups of young and old in each group showed interesting results (Table 2). In the subgroup analysis, there was no hemodynamic difference in 0.2% ropivacaine groups. However, in 0.75% ropivacaine group, there were significant differences in CVP, SVV, SVRI, and SVI between old and young subgroups although MAP was not differ. In 0.375% group, there were significant differences only in SVRI and SVI depends on the age.

Page 12-16 Discussion

Numerous sentences were modified and marked with red letters and underlining.

3. Both CVP and SVV are weak predictor for hypotension base on ROC curve.

A) SVV is considered to be a weak predictor because its sensitivity and specificity are low. Although SVV showed significantly higher sensitivity and specificity compared to that of CVP, but its AUC is somewhat low, 0.687. In case of TEA, the AUC is
Conclusions: High concentrations of ropivacaine caused severe hypotension and SVV changes, and these changes were more severe in the aged patients. SVV has a limited ability to predict hypotension following TEA, although SVV showed better correlation with hemodynamics than CVP.

Page 15

A few studies reported SVV is a useful predictor of potential hypotension during the early postoperative period following combination of general and epidural anesthesia. However, the reliability of SVV could still be an issue and need to be more investigated during TEA. In our study, although SVV was better than CVP, SVV was also weak as a prediction tool (AUC, 0.687) of subsequent hypotension following TEA.

5. Do all the patients have the similar NPO time?

A) Yes, there was no statistically significant difference. Moreover, we added fasting time in Table 1 and methods section.

Table 1 revised.

Revised manuscript is following:

Page 8.
Parametric data such as age, weight, height, fasting time and infused volume of crystalloid were analyzed by ANOVA.

Table 1 revised.

6. How is the data from Flotrac after initial preoperative fluid loading?

A) The patients were not in critical condition such as shock state. Thus, the administration of 10ml/kg did change SVV about 3-5%. Through the reported literature, the cut-off value of SVV to predict fluid responsiveness is 9%. Thus it can be said that no significant difference occurred after 10ml/kg of fluid administration before TEA.

6. Results: The second paragraph can be omitted for all the data are fully demonstrated in table 1. it's quite clear. The 3rd,4th, and 5th paragraph, that is something that should be shown in the discussion section.
A) I think you meant figure 2 rather than table 1. I corrected the part of results as your recommend. I briefly summarized the contents of figure 2 in second paragraph and I removed the contents associated with discussion in 3rd, 4th, and 5th paragraphs. Thank you for your good comments.

Revised manuscript is following:

Page 10-11

Results

Total of 109 patients with complete case report forms were analyzed. Eleven patients were excluded due to protocol deviations. Two from 0.75% ropivacaine group, 6 from 0.375% ropivacaine group and 3 from 0.2% ropivacaine group were excluded (Fig. 1). No statistically significant differences were seen among the groups regarding to age, sex, height, weight, ASA PS, fasting time, mean fluid administration until the end of the study, and type of surgery (Table 1). BIS and end-tidal sevoflurane concentration also showed no significant difference among the groups (P = 0.135 and P= 0.315, respectively).

In the aspect of concentration effect, MAP (P = 0.039) and SVRI (P = 0.026) were significantly decreased in 0.75% ropivacaine group compared with other groups. Concordant increase in SVV was remarkably increased in 0.75% group compared with 0.375% and 0.2% ropivacaine group through the study period (P=0.017). In contrast, HR (P = 0.114), CVP (P = 0.303), CO (P = 0.389), CI (P = 0.468), SV (P = 0.453), and SVI (P = 0.303) showed no significant difference among the groups.

Moreover, the proportion of patients who needed ephedrine was remarkably higher in 0.75% ropivacaine group (p = 0.04, Table 1).

Through the observation period in the same group, MAP (P < 0.001), SVRI (P = 0.009), and CI (P = 0.001) showed significant changes following time and lowest value at T10, whereas SVV (P = 0.031) showed distinct change, but the highest value at T10 compared with baseline value in 0.75% ropivacaine group. CVP (P = 0.012) and SVI (P = 0.309) showed no significant changes among the time points in 0.75% ropivacaine group. In contrast, these changes were not apparent in 0.375% and 0.2% ropivacaine group. Although there were significant changes in MAP (P < 0.001 in 0.375% and 0.2% ropivacaine group) and HR (P < 0.001 in 0.375% and 0.2% ropivacaine group) depend on time points, other hemodynamic parameters did not show significant changes following time (Fig. 2).

Hemodynamic data measured in two subgroups of young and old in each group showed interesting results (Table 2). In the subgroup analysis, there was no hemodynamic difference in 0.2% ropivacaine groups. However, in 0.75% ropivacaine group, there were significant differences in CVP, SVV, SVRI, and SVI between old and young subgroups although MAP was not differ. In 0.375% group, there were significant differences only in SVRI and SVI depends on the age.
MAP showed negative correlation with SVV (correlation coefficient -0.244, p < 0.001) and positive correlation with SVRI, whereas MAP showed no significant correlation with CVP (correlation coefficient -0.074, p = 0.051). Other Derivative hemodynamic parameters of SVV such as SV, SVI, SVRI, and CI were all correlated with SVV (Table 3).

Of the 109 patients, 66 were responders to 20% decrease of MAP at T20 after epidural loading and 43 were nonresponders (Table 4). Although hemodynamic parameters at T0 showed no difference between responders and nonresponders, SVV and MAP at T20 in responders were significantly different. The overall performance for SVV and CVP in predicting the 20% decrease of MAP was assessed by drawing ROC curves (Fig. 3). The AUC of SVV (0.687 [95% CI, 0.587-0.787]) was significantly large whereas AUC of CVP (0.477 [95% CI, 0.369-0.584]) showed non informative value (P = 0.026). The optimal cutoff value of SVV to distinguish between responders and nonresponders was 9.5% (sensitivity: 60.6%, specificity: 68.9%) at T20.

7. Can it be possible to do a subgroup analysis for aged patients?

A) Thank you for your comment. We conducted subgroup analysis depends on the age at 60. We revised the whole manuscript and added Table 2 of subgroup analysis.

Page 10-11

Results

Hemodynamic data measured in two subgroups of young and old in each group showed interesting results (Table 2). In the subgroup analysis, there was no hemodynamic difference in 0.2% ropivacaine groups. However, in 0.75% ropivacaine group, there were significant differences in CVP, SVV, SVRI, and SVI between old and young subgroups although MAP was not differ. In 0.375% group, there were significant differences only in SVRI and SVI depends on the age.

Page 12

Hypotension in the high concentration group was more prevalent in aged patients, and the accompanying SVV changes were more pronounced.

Page 13

We assumed that the incidence of hypotension was much higher because elderly patients were included more in the study of FDA report. Segmental dose reduction with increasing age after TEA has been well documented [16, 17]. Through the subgroup analysis depends on the age, we could confirm that the aged patients are vulnerable to high concentrations of ropivacaine during TEA. When high concentrations are used, the dose increases. Thus, we assumed that high dose of ropivacaine in elderly patients of 0.75% ropivacaine group caused the increase of block width and thus the hemodynamic effect of TEA was exaggerated.

Page 15.
In the subgroup analysis depends on the age, there was no hemodynamic difference in 0.2% ropivacaine groups. However, in 0.75% ropivacaine group, there were significant differences in CVP, SVV, SVRI, and SVI between old and young subgroups although MAP did not differ. SVRI after TEA was maintained higher in elderly patients, whereas reflex tachycardia was prominent in young patients. We assumed that the vascular reactivity after sympathetic block by TEA also could be an influencing factor of hemodynamic changes during TEA. In 0.375% group, there were significant differences only in SVRI and SVI depends on the age.

8. There is nothing about myocardial depression. and as demonstrated in your table, the MAP was 69.6 +/- 14.5 mmHg. Do you think it's harmful for patients?

A) You are right. There is no data about myocardial depression. Thus, we revised our manuscript. We do not think the MAP change after TEA is critical, because as you commented, the MAP was 69.6 +/- 14.5 mmHg and easily controllable by single administration of ephedrine. That would be nothing during anesthesia. However, after subgroup analysis depends on the age following your comment, now we can describe the elderly patients in use of high concentration of ropivacaine could be vulnerable to severe hypotension.

Revised manuscript is following:

Page 14

In our study, a reduction of MAP was regarded as a result of a decrease in SVR, but negative inotropic and chronotropic effect was not evident.

Page 14

Although we could not identify the extent of blockade, we intended epidural block from T4-5 to L1-2, which could have minimal effect on left ventricular function and cardiac conduction velocity. If the extent of blockade was high thoracic (T1-T4), negative inotropic and chronotropic effect might be more prominent following epidural loading dose.

9. By ROC curve, both SVV and CVP are both weak predictors for hypotension.

A) As mentioned above, we corrected the conclusion.

Revised manuscript is following:

Page 15

A few studies reported SVV is a useful predictor of potential hypotension during the early postoperative period following combination of general and epidural anesthesia. However, the reliability of SVV could still be an issue and need to be more investigated during TEA. In our
study, although SVV was better than CVP, SVV was also weak as a prediction tool (AUC, 0.687) of subsequent hypotension following TEA.

Reviewer 2)

1. Line 8 to 13: The cardiovascular depression that is observed during anesthesia may be due to general anesthesia or general as well as epidural analgesia. So this sentence needs to be revised or expressed in another way.

   A) I really appreciate you pointing out exactly. You are right. It’s my mistake. “Cardiac depression” is not what I want to say. I wanted to express the impairment of hemodynamics such as hypotension during TEA with general anesthesia.

Revised manuscript is following:

Background: Thoracic epidural anesthesia (TEA) exacerbates hypotension due to peripheral vasodilator effects following use of general anesthetics. This study was aimed to compare of hemodynamic changes by three different concentrations of epidural ropivacaine and to evaluate the performance of stroke volume variation (SVV) and central venous pressure (CVP) during TEA with general anesthesia.

2. Line 13-15: Is this sentence may describe your concerns more clearly?

   A) I really appreciate your wonderful expression. I modified this sentence according to your recommendation.

Revised manuscript is following:

Background: Thoracic epidural anesthesia (TEA) exacerbates hypotension due to peripheral vasodilator effects following use of general anesthetics. This study was aimed to compare of hemodynamic changes by three different concentrations of epidural ropivacaine and to evaluate the performance of stroke volume variation (SVV) and central venous pressure (CVP) during TEA with general anesthesia.

3. Line 16 to 18: What do you mean by static and dynamic hemodynamic parameters?

   A) We wanted to evaluate the changes of hemodynamic parameters due to three different dose of epidural ropivacaine during general anesthesia. These parameters included dynamic parameters such as SVV as well as static parameters such as BP and CVP. SVV has been used recently as one of dynamic preload parameter in ICU and operating room. However, the effect of TEA during general anesthesia on SVV is not well evaluated. We wanted to know changes and relations of these parameter. And we wanted to know if SVV or CVP could be a predictive parameter for hypotension developing during TEA.
with GA. However, we think you are right. We agree with your advice that hypothesis or aim should be simple. Therefore we modified this sentence according to your recommendation.

Revised manuscript is following:

Page 2

Background: Thoracic epidural anesthesia (TEA) exacerbates hypotension due to peripheral vasodilator effects following use of general anesthetics. This study was aimed to compare of hemodynamic changes by three different concentrations of epidural ropivacaine and to evaluate the performance of stroke volume variation (SVV) and central venous pressure (CVP) during TEA with general anesthesia.

4. Line 38: SVV and CVP…….should be corrected as:

SVV, CVP and measurement of mean arterial pressure following epidural loading with a 20% decrease

A) Thank you for kind correction. I corrected as your recommendation.

Revised manuscript is following:

Methods: One hundred and twenty patients were randomly divided into three groups to epidurally receive 8 ml of 0.75%, 0.375%, or 0.2% of ropivacaine. Hemodynamics were monitored for 30 min after loading. We analyzed hemodynamic changes in subgroups according to age at 60. Receiver operating characteristic (ROC) analysis was performed to characterize the relationship between SVV, CVP and 20% decrease in mean arterial pressure (MAP) following TEA.

5. Conclusion

It is not well written, What are your findings for each given döşe is actually more important in my opinion. Because the two first concentrations and doses of ropivacaine are more commonly used as a bolus dose. Epidural ropivacaine infusion has more effects on hemodynamics instead of bolus doses. If you can provide that data and Show their effects on SVV, that should be published because there is little data on effects of epidural ropivacaine on SVV. High dose effects on hemodynamics is not something that is not shown before so this should not be your conclusion. CVP is not informative, this can be stated in a separate sentence. What do you mean by improvement of accuracy is not also clear. I think this can not be a conclusion in your study. You are not evaluating accuracy. You are using only epidural bolus doses and looking for differences in hemodynamics by the use of CVP and SVV. Than you should state this for goal and find a result in this line and present in conclusion and findings. High dose of epidural ropivacaine caused bigger change of hemodynamic parameters due to the change of SVR. SVV could be more informative than CVP, however improvement of accuracy needed for detection of hemodynamic changes in TEA. I should state that the whole text needs to be revised according to the abstract. Your goal is to investigate a correlation between 20% decrease in MAP and
epidural loading dose of ropivacaine, than your result and conclusion needs to state these. Make a hypothesis first and investigate your hypothesis. How do you get the conclusion that an improvement of accuracy is needed for detection of hemodynamic changes? From your results. Please explain. Because of some major mistakes in abstract and methods including expression of your hypothesis to the reader, it is my point of view that you should rewrite the manuscript before sending for reevaluation.

Thank you.

A) Thank you for kind suggestion and scrupulous comments. We agree with you about the limitation of our study. We revised the conclusion and added subgroup analysis depends on the age at 60 at Table 2. As your comment, we revised the conclusion and the whole manuscript about the limit of predictability of SVV and CVP. SVV is considered to be a weak predictor because its sensitivity and specificity are low. Although SVV showed significantly higher sensitivity and specificity compared to that of CVP, but its AUC is somewhat low, 0.687. In case of TEA, the AUC is lower than that of published literature, 0.85-0.72. These points were revised in the manuscript.

Revised manuscript as follows:

Page 15.

A few studies reported SVV is a useful predictor of potential hypotension during the early postoperative period following combination of general and epidural anesthesia. However, the reliability of SVV could still be an issue and need to be more investigated during TEA. In our study, although SVV was better than CVP, SVV was also weak as a prediction tool (AUC, 0.687) of subsequent hypotension following TEA.

In our data, SVV was acceptable as an ancillary prediction tool (AUC, 0.687) and optimal threshold to differentiate between responders and nonresponders was 9.5% (sensitivity of 60.6% and specificity of 68.9%). The reported guideline for accuracy of diagnostic system, AUC should be above 0.7 [25]. AUC of SVV after TEA was 0.687 and thus it could be considered weak as an indicator to predict subsequent hypotension in our study.

A) We have conducted a preliminary study comparing epidural loading dose with slow infusion and bolus infusion according to your opinion. However, as reported in the literature, blood pressure decreased depends on the LA dose administered epidurally. However, when the loading dose was administered over 30 minutes, the time of hypotension occurred in 40-50 minutes, unlike hypotension in 10-20 minutes. It was interesting. We could conduct that study in the future with the appropriate number of samples. Unfortunately, in this study, it is difficult to add those study because such methods are not registered in the IRB or clinical trials. Please consider that.
A) We revised abstract first and revised the whole manuscript to clarify our hypothesis following your comment. Please read the red text with underlined throughout the whole manuscript.

What do you mean by improvement of accuracy is not also clear. I think this can not be a conclusion in your study. You are not evaluating accuracy. You are using only epidural bolus doses and looking for differences in hemodynamics by the use of CVP and SVV. Than you should state this for goal and find a result in this line and present in conclusion and findings.

A) We thought that ROC analysis of SVV showed predictive ability for 20% decrease in MAP, albeit weakly. Therefore, we intended to say that there is a relationship but, it is statistically weak. We agree with your opinion. Improvement of accuracy cannot be a conclusion. We removed this sentence from conclusion. We described the relation between epidural loading dose and hemodynamic changes as conclusion according to your recommendation. Thank you for sincere recommendation.

Revised manuscript is following:

Page 15.

Our observations support the hypothesis that the hemodynamic variables are affected by the concentration of epidurally administered ropivacaine. High concentrations of ropivacaine caused severe hypotension and SVV changes, and these changes were more severe in the aged patients. SVV has a limited ability to predict hypotension following TEA, although SVV showed better correlation with hemodynamics than CVP.

6. I should state that the whole text needs to be revised according to the abstract.

A) Thank you very much. We revised whole manuscript following changed abstract following reviewers’ comment. Please read whole manuscript revised, it was marked as red color with underline.

Reviewer 3)

1. Abstract

- Please better specify in the "conclusion" if "the high dose" or "High concentrations" of epidural ropivacaine…. 

A) Thank you for your helpful comments. We changed the whole manuscript to clarify our hypothesis following your comments. From the title “Observations on
significant hemodynamic changes caused by high concentration of epidurally administered ropivacaine: Correlation and prediction study of stroke volume variation and central venous pressure in thoracic epidural anesthesia” to discussion section, the whole manuscript was revised. Please read whole manuscript revised, it was marked as red color with underline.

2. Introduction

Please specify the aim of the study and clinical message that the authors want to send
A)

Revised manuscript is following:

Page 3.

In current study, we tested the hypothesis that hemodynamic derangement following TEA is more significant in use of higher concentration of LA, which was administered in patients undergoing major upper abdominal surgery. Additionally, we evaluated the SVV could be a diagnostic parameter for detection of hemodynamic derangement after TEA combined general anesthesia.

3. Materials and Methods

- Please specify if they were followed the Consort guidelines

A) Yes, we followed the consort guidelines. We revised the whole manuscript section. Please read that. Moreover, we attached consort checklist file.

- Allocation/randomization: please, better specify

A)

Revised manuscript is following:

Random numbers were made by computer and used to distribute the subjects into their groups. The allotment took place after induction of anesthesia. The study solution was prepared according to distributed group and blinded by an anesthetic nurse investigator who does not participate in anesthesia. Therefore, the induction anesthesiologist was unaware of the drug concentration.

- Please better specify if there are missing data

A) We described the missing data from each group, and this is also shown in Fig. 1.

Revised manuscript is following:
Eleven patients were excluded due to protocol deviations. Two from 0.75% ropivacaine group, 6 from 0.375% ropivacaine group and 3 from 0.2% ropivacaine group were excluded (Fig. 1). No statistically significant differences were seen among the groups regarding to age, sex, height, weight, ASA PS, fasting time, mean fluid administration until the end of the study, and type of surgery (Table 1).

4. Discussion

- please specify the aim of the study and clinical message that the authors want to send

A) This study was aimed to compare of hemodynamic changes due to three different concentration of epidural ropivacaine during general anesthesia. We found there were significant MAP change and SVR change in 0.75% epidural ropivacaine. Therefore we need careful monitoring and vasopressors for hemodynamic stability when 0.75% ropivacaine administered epidurally during general anesthesia. Although, SVV showed negative correlation with MAP, SVV was weak to be a prediction tool of potential hypotension. We described this in detail throughout the discussion section.

5. References

Please check the journal's guidelines

A) I have checked the journal’s guidelines and corrected ref. 15

Revised manuscript is following: