

Dear Editors and Reviewers,

Thank you for reading our manuscript with interest and sharing your valuable opinions. I believe your comments will be a great help to improve our manuscript. Here are my responses to your comments; I replied for the issues one-by-one and attached the revised parts in our manuscript for your convenience.

**Reviewer #1**

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:**

A small amount of propofol itself induces vasoconstriction then a low dose of propofol to avoid hypotension during induction could cause hypertension with tachycardia. In this case, there were several instances in which blood pressure increased following propofol administration. Although it is widely known that propofol generally reduces blood pressure, its reverse mechanism for increasing BP has not been established, and related case reports are rare. Well discussed and clearly written.

**Responses to Reviewer:**

Thank you for favorable comments to our manuscript.

**Reviewer #2**

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** No

**Responses to Reviewer:**

Thank you for favorable comments to our manuscript.

### **Reviewer #3**

**Conclusion:** Major revision

#### **Responses to Reviewer:**

I really appreciate your deep interest in our manuscript and sharing your knowledge as well as detailed opinions. Also, I agree all the issues raised in your review are critical. Here are added or revised contents below according to your feedback.

#### **Issue #1: A diagnosis of exclusion**

I totally agree with your opinion; it should be a diagnosis of exclusion, especially in our case. We added other possibilities which could cause perioperative hypertension and described one-by-one in detail; psychological factors, pheochromocytoma, undiagnosed essential hypertension, thyrotoxicosis, and wakefulness or insufficient depth of anesthesia (Page 6/paragraph 59, and from page 7/paragraph 4 to page8/paragraph 4).

#### **Issue #2: Pheochromocytoma**

We evaluated the possibility of undiagnosed pheochromocytoma was low in our case because BP was consistently high above the normal range without fluctuation, regardless of the surgical stimulation, which is not consistent with clinical manifestations of pheochromocytoma; BP fluctuates widely in normal range in patients with pheochromocytoma as you mentioned in review. Stabilized BP after suspending propofol and switching to sevoflurane also suggested a low possibility of pheochromocytoma. (Page 8/paragraph 3)

#### **Issue #3: Thyrotoxicosis**

Our patient had not complained any symptom of thyrotoxicosis and there was no preoperative thyroid manipulation. In addition, preoperative thyroid hormone levels were normal. We had not mentioned thyrotoxicosis in our first manuscript because we considered its possibility very low, however, we decided to describe these circumstances in our revised manuscript for a diagnosis of exclusion. (Page

8/paragraph 4)

#### **Issue #4: Undiagnosed essential hypertension**

We considered undiagnosed essential hypertension or whitecoat hypertension because it is a common cause of uncontrolled high blood pressure. We described that in our first manuscript; the patient had no past medical history including hypertension and her preoperative blood pressure at the ward was well controlled without administration of antihypertensive drugs. Reflecting your feedback, we described the preoperative scene in detail rather than jumping on intraoperative scene; including the psychological status of the patient, physical examination and radiological examinations suggesting her blood pressure was well controlled. (Page 3 '*Clinical presentation*', page 4/the first paragraph of '*intraoperative events*', and page 7/paragraph 4)

#### **Issue #5: The mechanism of propofol-induced hypertension and cardiac monitoring**

As you pointed out, even though we placed an arterial catheter, a pulse contour analysis or cardiac Doppler device was not used; regrettably, the cardiac index was not monitored. Therefore, the HR was the only variable we observed, and stroke volume as well as systemic vascular resistance could not be measured. If the blood pressure had remained consistently high after invasive blood pressure monitoring, we would have conducted a pulse contour analysis or cardiac Doppler, however, at the time of invasive BP monitoring, BP was normalized. We clarified those in our revised manuscript. (Page 7/paragraph 3)

#### **Issue #6: Labetalol**

We agree with your comment; 10mg of labetalol is not a high dose considering its dose regimen. However, we administered labetalol 10mg twice 5 min interval, and we avoided the administration of a higher dose to prevent a sudden hypotension, considering her preoperative blood pressure was not high and high concentrations of intravenous anesthetics were administered at that time. We think the vasodilative effect of labetalol as a non-selective alpha/beta-antagonist was suppressed by

vasoconstriction caused by high concentrations of propofol. (Page 7/paragraph 1)

Sincerely,

Hae Jeong Jeong