



Reply to the letter by Parker G. Allan

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We were grateful to Allan PG et al. [1] for having interest in our manuscript [2].

First, we should apologize that we overlooked the missing of ‘ μ ’ in unit of fentanyl in the published article in several places. Correction had already been published in the Journal [3].

As to the fentanyl administration, our method is quite along with our routine clinical practice. It is known that effect-site concentration (Ce) of 4–5 ng/mL were required to minimize the hemodynamic changes during intubation and at incision for fentanyl [4]. Then we administered 3 μ g/kg of fentanyl before intubation, and 2 μ g/kg of fentanyl before incision (totally 5 μ g/kg). Then we added 1 μ g/kg of fentanyl on requirement during surgery. According to our method, Ce of fentanyl was kept 1.0–3.0 ng/mL in most cases. For example, Ce of fentanyl was 1.5–3.5 ng/mL during surgery in the case shown in Fig. 1. Larger dose of fentanyl might be effective to block noxious stimuli, but it might cause respiratory depression after surgery considering the metabolic rate of fentanyl.

They highlighted the sensitivity and specificity of pBIC as a reliable indicator of sufficient analgesia. However, as stated in our manuscript, our method is not always suitable for all patients. It works best for patients who show

high pBIC values at the surgical level of anesthesia before incision. Most patients under 50 showed noticeable pBICs (> 40%), and 70–80% of those aged 50–65 also had high pBICs (> 30%). However, older patients generally showed smaller pBIC peaks. Here, we are focusing only on patients who had high pBICs before incision. In these patients, pBIC sensitivity was nearly 100%, meaning that when pBICs were high, analgesia was considered adequate.

We calculated the specificity for four criteria: 0.86 (LT10high), 0.85 (LT10low), 0.92 (BL20high), and 0.84 (BL20low). This was based on a significant increase in pBIC values from AddFent to Post5, indicating high specificity. In the previous report [5] with 24 patients at incision, both sensitivity and specificity were 100%. In that study, 3 μ g/kg of fentanyl was added after incision, effectively blocking noxious stimuli in all cases. We believed that 1 μ g/kg of fentanyl was not always enough to block noxious stimuli during surgery because the intensity of surgical stimuli can change rapidly, and this dose may be insufficient in some cases. Of course, we must always consider other possible causes for decreased pBICs beyond insufficient analgesia. Allan PG et al. [1] noted that pBIC could be influenced by various factors, including drugs, pain stimuli, and hemodynamic changes. However, we think that hemodynamic changes themselves do not directly affect pBICs unless it was caused by noxious stimuli, as explained in our manuscript. Of course, other factors that might change pBICs must be excluded when we use pBICs as the indicator for adequacy of analgesia, as we discussed in our manuscript. We thought it was not difficult in the clinical practice.

In the current study, we added fentanyl while the criteria were not satisfied. This was caused by the mistake of our study method. Our software merely showed pBIC values and their trend figures, then it was difficult to correctly judge whether the criteria were fulfilled or not. It was our fault.

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We would try to modify our software to check the criteria automatically.

They also highlighted gender differences and types of surgery. Actually, in the current study, most included patients were female, and most of the surgery were laparoscopic gynecological surgery. However, one of the authors (SH) used the software BSA for more than 20 years in routine clinical practice, and observed the changes of pBICs in various situations, and found similar results also for male patients and other types of surgery. The reason why we mainly selected laparoscopic surgery was that the changes of surgical stimuli seemed rather small compared with open surgery, and therefore addition of 1 µg/kg of fentanyl would be sufficient in most cases.

They also criticized us for not specifying the amount of fentanyl used. We believed that focusing on the amount of fentanyl is less meaningful in clinical practice. It varied depending on the duration of the surgery and anesthesia. Clinicians should always consider Ce of opioids. They also mentioned the minimum alveolar concentration (MAC), but we believe the MAC concept is outdated. Of course, we should still consider the interaction of anesthetic with opioids. We thought that we should aim both adequate level of hypnosis and adequate analgesia in the concept of ‘balanced-anesthesia’. Katoh et al. [4] showed that isobolograms for MACawake, MAC and MACbar were shaped differently, which indicated that every combination of sevoflurane and fentanyl is identical considering multiple endpoints of anesthesia (prevention of awareness, prevention of memory, prevention of movement, prevention of autonomic responses, etc.). We do not believe that either ‘deep hypnosis with low opioid doses’ or ‘light hypnosis with high opioid doses’ is adequate. Anesthesiologists should consider the anesthetic state from physiologic point of view. Prevention of body movement is not the ultimate goal of general anesthesia.

They also pointed out that we did not have a control group. Primarily, we did not think that total consumption of opioid is important, because conclusion of such comparison depended on the quality of ‘control group’. If the control group’s methods are poor, the result will be positive. Conversely, if the control group’s methods are sophisticated, the result will be negative. Non-invasive blood pressure (NIBP) was measured every 2.5 min, as is standard in our clinical

practice, which might cause slight timing discrepancies in NIBP data collection. However, heart rate was monitored in real time.

Anyway, pBICs were more sensitive to noxious stimuli compared with the response of autonomic nervous system. The problem is that our method can be applicable only in patients who showed high pBICs before incision.

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Data availability The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest None.

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