Contralateral cerebral hemoglobin oxygen saturation changes in patients undergoing thoracotomy with general anesthesia with or without paravertebral block: a randomized controlled trial

Short title: Surgical incision and cerebral oxygen saturation

Keika Mukaihara, Maiko Hasegawa-Moriyama*, Yuichi Kanmura

Department of Anesthesiology and Critical Care Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan

Keywords

Surgical incision, cerebral oxygen saturation, near-infrared spectroscopy

Word count of the whole manuscript: 3994

Number of tables: 4

Number of figures: 5

***Corresponding author**

Maiko Hasegawa-Moriyama

Department of Anesthesiology and Critical Care Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan.

Tel: +81-99-275-5430

Fax: +81-99-265-1642

E-mail: hase-mai@m3.kufm.kagoshima-u.ac.jp

This work should be attributed to

Department of Anesthesiology, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan.

Disclosure of funding

N/A

Contact information for the Institutional Review Board that approved our study

Ethics Committee of Kagoshima University Hospital.

8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan

E-mail: soumud@kuas.kagoshima-u.ac.jp

Tel: +81-99-275-6691

Abstract (239 words)

Purpose: Perioperative analgesia during thoracotomy is often achieved by combining paravertebral block (PVB) with general anesthesia (GA). Functional near-infrared spectroscopy (NIRS) can detect changes in cerebral oxygenation resulting from nociceptive stimuli in the awake state or under sedation. We used NIRS to measure changes in cerebral blood flow provoked by thoracotomy incision made under GA and determine how these changes were influenced by supplementation of GA with PVB.

Methods: Thirty-four patients undergoing elective thoracotomy were enrolled. Patients were randomly assigned to a group receiving only GA, or GA combined with PVB (GA+PVB). Changes in cerebral oxygenated hemoglobin (ΔO_2Hb), deoxygenated-Hb (ΔHHb), and total-Hb (ΔtotalHb) were evaluated by NIRS as surgery began.

Results: In the GA group, ΔO_2Hb was significantly higher in the hemisphere contralateral to the side of surgery when the incision was made and 2 min after incision compared with the ipsilateral side (start of surgery, $P < 0.01$; 2 min, $P < 0.05$). In contrast, there were no significant changes in the ΔO_2Hb at any of the time points in the GA+PVB group. Comparable with ΔO_2Hb, the concentration of ΔtotalHb was significantly higher in the contralateral hemisphere in the GA group at the start of surgery ($P < 0.05$).

Conclusions: Changes in the cerebral O_2Hb concentration were detected by NIRS immediately after surgical incision under GA, but not in the presence of a PNB. NIRS could be used to monitor surgical pain. PVB inhibited changes in oxygenation induced by incision-provoked pain.

Introduction

Various anesthetic and analgesic strategies are available to address surgical pain. However, because of the lack of objective monitoring to evaluate pain intensity during anesthesia, the optimal analgesic strategy remains debatable even when hemodynamic changes are not detected during the surgical procedure.

The neural network underlying the perception of acute and chronic pain is now well understood (1). The main components of the pain matrix are the primary and secondary somatosensory cortices (S1 and S2, respectively), insular cortex, anterior cingulate cortex (ACC), prefrontal cortex (PFC) and the thalamus. In addition to the ACC, an increase in local blood flow in the PFC is thought to reflect activation of the attentional and memory networks by noxious stimulation. Activation of the PFC is consistently associated with pain perception in chronic pain states such as neuropathic pain (2).

Noxious stimuli administered to healthy subjects are also reportedly accompanied by an increase in PFC activity (1), when pain is provoked by capsaicin treatment (3), trauma (4), underlying visceral pain such as angina pectoris (5), and abnormal intestinal pain (6), suggesting that surgery might also induce activation of the PFC. Indeed, functional magnetic resonance imaging (fMRI) has shown that surgical incision induces activation of the frontal area, including Brodmann area 10 (BA10), predominantly in the contralateral cerebral hemisphere (7). In contrast with fMRI, near-infrared spectroscopy (NIRS) may be used to non-invasively monitor tissue oxygenation and cerebral blood flow during anesthesia. Functional NIRS has shown that neuromuscular electrical stimulation of the forearm extensor muscles significantly increases activation in the

cortical layer of the contralateral sensorimotor network including the PFC (8). Yennu *et al.* also demonstrated that acute pain induced by thermal stimulation of the right forearm, right temporomandibular joint and left forearm induced significant increases in the oxyhemoglobin concentration in the PFC, which was detectable by NIRS (9).

More recently, NIRS has been used to detect changes in cerebral blood flow during sedation and general anesthesia (GA). In patients undergoing colonoscopy while sedated with midazolam, the pattern of activation of the pain matrix evaluated by functional NIRS was similar to that previously observed after noxious stimuli in healthy, awake individuals (10). It has been proposed that NIRS could be a useful means of evaluating brain activity evoked by noxious stimuli under sedation or when incomplete analgesia has been achieved. Kussman *et al.* reported that frontal cortical signals evoked during catheter ablation of arrhythmia under GA with sevoflurane were detected by NIRS positioned on the forehead, which was consistent with the changes induced by noxious stimulation in healthy volunteers (11).

However, it is not clear whether nociceptive input to the brain can induce unilateral changes in cerebral blood flow under general anesthesia during surgery, even when hemodynamic changes such as elevations in the heart rate and blood pressure are not detectable, or whether NIRS can detect PFC activation under general anesthesia.

Regional anesthesia techniques such as epidural or peripheral nerve blocks may often be combined with general anesthesia for perioperative and postoperative analgesia. However, the impact of neuraxial or nerve block in cerebral pain processing during anesthesia has not been investigated. In this study, we examined whether NIRS

measured on the forehead can detect changes in frontal cerebral oxygenation induced by surgical incision and whether paravertebral block (PVB) can abolish these changes in patients undergoing thoracotomy.

Methods

Patients

This study was approved by the Ethics Committee of Kagoshima University Hospital, and written consent was obtained from all participants. From August to November 2016, patients scheduled for elective video-assisted thoracic surgery were enrolled in this randomized contolled trial (UMIN000024263). The exclusion criteria were an American Society of Anesthesiologists physical status of > Ⅲ, central or peripheral neuropathy, allergy to local anesthetics, or coagulopathy.

Protocol

Patients were randomly assigned to one of two groups using Research Randomizer version 4.0; those who underwent GA only (GA group) and those who underwent both GA and thoracic PVB (GA+PVB group). Blood oxygen saturation (SpO_2) was measured by a pulse oximeter placed on the same side as the surgery, and a catheter was inserted into the radial artery on the opposite side. A specimen of arterial blood was used for acid-base and blood gas analysis. A regional oxygen saturation monitor (NIRO-200^{TM}; Hamamatsu Photonics, Hamamatsu, Japan) and bilateral bispectral index (BIS) sensors (Covidien/Medtronic, Minneapolis, MN, USA) were applied to the forehead during anesthesia. The sensor for measurement of regional oxygen saturation was placed over BIS sensors. Data for the NIRO-200^{TM} monitor were sampled in 10-s intervals, while those for the BIS were sampled in 15-s intervals.

In the GA group, an epidural catheter was directed cephalad through a 17-gauge Tuohy needle introduced through the Th6/7 or Th7/8 interspace. A test dose of 2 ml of 1% mepivacaine was injected before induction of GA. Anesthesia was induced with an effect-site target-controlled infusion (TCI) of propofol at 4 μg/ml, remifentanil at 0.5 μg/kg/min, and rocuronium at 0.6 mg/kg. After bag-mask ventilation with a facemask using 100% oxygen at a fresh gas flow of 6 L/min, the trachea was intubated with a double lumen tube. After intubation, the patients were mechanically ventilated to maintain the end-tidal carbon dioxide tension at 35 to 40 mmHg with a fraction of inspired oxygen of 0.6. Anesthesia was maintained with continuous intravenous TCI of propofol with an effect site concentration of 2.5 to 4.0 μg/ml to maintain the BIS at 40 to 60. Remifentanil was administered at 0.2 to 0.5 μg/kg/min. Rocuronium boluses were administered as necessary, guided by a train-of-four monitor (TOF Watch; Nihon Kohden, Tokyo, Japan). After positioning the patient in the lateral decubitus position, the NIRO-200 device was set to zero. In the GA+PVB group, an 18-gauge Tuohy needle was inserted perpendicularly into the skin at the level of the Th5/6 or Th6/7 interspace and advanced 2.5 cm laterally until the tip of the spinous process was reached. The needle was then withdrawn slightly and redirected cephalad at a 45-degree angle to the skin up to 1.5 cm further than the depth of bone contact. The catheter was inserted through the needle 1 to 2 cm beyond its tip. A test dose of 2 ml of 1% mepivacaine was injected, and 25 ml of 0.3% ropivacaine was then administered before the start of surgery. The skin was incised at the sixth to eighth intercostal space at the start of surgery. Neither fentanyl nor a local anesthetic was given before the surgical

specimen was resected. Assessment of sensory blockade by PVB was performed at each dermatome level by checking loss to pinprick, cold, and light touch sensation at the end of anesthesia.

NIRS measurement

The NIRO-200^{TM} (Hamamatsu Photonics) uses three wavelengths of near-infrared light (755, 810 and 850 nm), and the sensor contains a laser diode and two detectors placed at 3.7 and 4.3 cm from the source of emitting light. The oximeter probes were placed on both sides of the forehead with the caudal border 1cm above the eyebrow, positioning the light source and sensors away from the frontal sinuses. The monitor uses spatially resolved spectroscopy methodology that combines multi-distance measurements of optical attenuation. This methodology enables the NIRO-200 to calculate the tissue oxygen index (TOI) using the following formula: $[O_2Hb/ (O_2Hb + HHb)] \times 100$, which is expressed as a percentage (%). Oxygenated hemoglobin (O_2Hb) and deoxygenated hemoglobin (HHb) are used to calculate the change in the total hemoglobin concentration (totalHb) using two wavelengths of near-infrared light and light-sensitive photodiodes. Based on the change in intensity of both wavelengths, the change in each chromophore concentration can be calculated using the modified Beer–Lambert law. Changes in the O_2Hb, HHb, and totalHb concentrations and the TOI were measured in both cerebral hemispheres at the following time points: 1 min before the incision, at the time of the incision, 1 min after the incision and 2 min after the incision.

Statistical analysis

Values are presented as the mean ± standard deviation. We uperformed a power analysis based on our preliminary study of 10 patients. We expected a 0.7 μmol/L difference in the change in O_2Hb between the ipsilateral and contralateral hemispheres at incision, and calculated a sample size of 17 patients per group for this study assuming $\alpha = 0.05$ (two tailed) and $\beta = 0.95$ (G*Power3; Heinrich-Heine-University, Dusseldorf, Germany). Differences in NIRS values were analyzed by two-way analysis of variance followed by Bonferroni's *post hoc* test for multiple comparisons. Differences in patients' demographic and clinical characteristics, physiologic and hemodynamic variables, and the dose of anesthetics were evaluated using the Mann–Whitney U test or Fisher's exact test. All statistical analyses were conducted using GraphPad Prism software (version 6.0; GraphPad Software, La Jolla, CA, USA). A *P* value of <0.05 was considered statistically significant.

Results

Thirty-four consecutive patients were enrolled, and none were excluded. There were no major perioperative complications. There were no significant differences in the groups' demographic or clinical characteristics (Table 1). There were also no significant differences in the acid-base status, including pH, the arterial partial pressures of oxygen and carbon dioxide; or the blood hemoglobin concentration at the start of surgery between the GA and GA+PVB groups (Table 2). Although the dose of propofol administered by TCI was not significantly different at each study time point, the dose of remifentanil was significantly lower in the GA+PVB group ($P < 0.05$) (Table 3). At each time point, the SpO_2, systolic blood pressure (sBP), and heart rate did not change significantly, and there were no significant differences between the groups (Table 4). The total number of segments blocked was 3.5 ± 1.9 at the end of anesthesia in all patients of GA+PVB group.

In the GA group, ΔO_2Hb in the hemisphere contralateral to the side of surgery was significantly higher at time of incision ($P < 0.01$) and 1 min after the incision ($P < 0.05$) compared with ΔO_2Hb 1 min before the incision (Fig. 1a). In contrast, ΔO_2Hb monitored in the ipsilateral hemisphere did not change significantly at any of the time points compared with 1min before surgery. The ΔO_2Hb was significantly higher in the contralateral hemisphere at the time of incision ($P < 0.05$) and 2 min after the incision ($P < 0.05$) compared with the ipsilateral side. In the GA+PVB group, ΔO_2Hb was significantly lower 1 min and 2 min after the incision in both the ipsilateral and

contralateral hemispheres ($P < 0.01$ for both) (Fig. 1b), but there was no difference in ΔO_2Hb between the hemispheres.

In contrast with the increase in ΔO_2Hb, ΔHHb monitored in the contralateral hemisphere was significantly lower 1 min ($P < 0.01$) and 2 min ($P < 0.05$) after the incision compared with 1min before the incision in the GA group, but there was no significant difference between the hemispheres (Fig. 2a). In the GA+PVB group, ΔHHb was significantly increased in the contralateral hemisphere 2 min after the incision and in the ipsilateral hemisphere 1 and 2 min after the incision ($P < 0.01$ for all comparisons). In the GA+PVB group, there were no differences between the ipsilateral and contralateral hemispheres at any time point (Fig. 2b).

Consistent with the increase in ΔO_2Hb at the start of surgery, ΔtotalHb in the contralateral hemisphere of patients in the GA group rose significantly at the time of incision compared with 1 min before the incision ($P < 0.01$) and was significantly higher in the contralateral than ipsilateral hemisphere at the time of incision ($P < 0.05$) (Fig. 3a). In the GA group, there were no significant changes in ΔtotalHb in the ipsilateral hemisphere at any of the study time points. In the GA+PVB group, despite the changes inΔO_2Hb and ΔHHb in both hemispheres 1 min and 2 min after the incision (Fig. 2b), ΔtotalHb did not change significantly at any of the time points (Fig. 3b).

There were no significant differences in ΔTOI at any of the time points in either hemisphere in the GA group (Fig. 4a), but ΔTOI was significantly lower 1 and 2 min after the incision compared with 1 min before the incision in both hemispheres ($P < 0.01$ for both) in the GA+PVB group (Fig. 4b).

The bilateral BIS were simultaneously monitored in this study (Fig. 5). In the GA group, the BIS values were significantly decreased on both sides 1min after the start of surgery ($P < 0.01$ for contralateral side and $P < 0.05$ for ipsilateral side) and 2 min after the incision on the ipsilateral side ($P < 0.05$) (Fig. 5a). In contrast, the changes in BIS were not statistically significant in the GA+PVB group (Fig. 5b).

Discussion

We found that ΔO_2Hb and Δtotal Hb rose and ΔHHb fell with the noxious stimulus of the thoracotomy incision in the cerebral hemisphere contralateral to the surgical site in patients undergoing GA with propofol and remifentanil (Figs. 1a, 2a, and 3a), although these changes in ΔO_2Hb and ΔtotalHb were not reflected in any changes in the TOI (Fig. 4a). These results suggest that cerebral blood flow in the contralateral frontal region is increased by surgical incision, peaking at the time of the incision before returning to the baseline level 2 min later (Fig. 1a). The localized cerebral hemodynamic response, including the increase in ΔO_2Hb, is reportedly correlated with the intensity of pain stimulus. A gradually increasing intensity of stimulation increases the peak frontal oxyhemoglobin saturation in a dose-dependent fashion, but a continued constant intensity of stimulation thereafter results in a gradual decrease in perceived pain and frontal NIRS signal (12, 13). Habituation of the local cerebral hemodynamic response to repeated noxious stimuli might partly explain our finding that the increased ΔO_2Hb in the contralateral hemisphere was transient (Fig. 1a).

In this study, the application sites of both the BIS and NIRS sensors presumably corresponded to the medial PFC; the sensors were located from Fp1 to F3 (left) and from Fp2 to F4 (right) based on the 10-20 system for placement of scalp electrodes in electroencephalography. The superior frontal cortex (BA 8–10), which is likely to correspond to the application sites of the sensors, was activated by an incision and partly positively correlated with the perception of ongoing incisional pain. This suggests

that parts of the prefrontal cortex play an important role in the processing of incision-induced pain.

In contrast to the increase in ΔO_2Hb after the incision in our study, or that by noxious stimuli in other reports, a decrease in ΔO_2Hb can also reportedly be brought about by noxious stimuli in awake volunteers (13) and by stretching of the colon during insufflation under sedation with midazolam (10). In the latter study, insufflation of the colon decreased ΔO_2Hb in the PFC, which returned to baseline levels a few seconds later. The decrease in O_2Hb was observed approximately 1.2 ± 3.0 s before the grimace response; this was likely indicative of deactivation of medial PFC neurons following the initiation of the pain stimulus (10). These results are nonetheless partly consistent with ours in that ΔO_2Hb returned to baseline levels shortly after the stimulus. An increase in medial PFC activation can be observed during episodes of sustained, intense ongoing pain (14), whereas increased lateral PFC activation is associated with a decreased pain effect, possibly by inhibition of functional connectivity between the medial thalamus and midbrain (3). In the present study, the time course of the decrease in ΔO_2Hb observed 1min and 2 min after the incision was delayed compared with the previous report(10, 12). Anesthetics including remifentanil may delay or impair the inhibitory cerebral changes induced by noxious stimulation.

Although a decrease in PFC blood flow in response to an acute pain stimulus has not been demonstrated by fMRI or positron emission tomography (PET), the inhibition of the PFC might be partly explained by the inhibitory pathways of pain perception, in which glutamatergic afferents from the amygdala monosynaptically innervate

GABAergic interneurons in the medial PFC, which synapse on layer V pyramidal cells and control pyramidal cell output. Therefore, medial PFC deactivation during pain stimulus may be the result of amygdala-driven feedforward inhibition of pyramidal cells as previously reported (15). The delayed decrease in ΔO_2Hb observed in the GA group might have been due to blocking of feedforward inhibition by propofol. Similar to other anesthetic agents, propofol can interfere with dendritic signal conduction in pyramidal neurons, leading to unconsciousness and resulting in decreases in connectivity along sensory pathways in the entire system (16).

After the PVB was performed, ΔO_2Hb and ΔTOI fell and ΔHHb rose significantly in both hemispheres 1 and 2 min after the incision compared with 1min before the incision, implying that these bilateral changes are not dependent on the lateral decubitus position or the PVB. This finding could be explained by the lower dose of remifentanil at all time points in the GA+PVB than GA group (Table 3). One transcranial Doppler study revealed that cerebral autoregulation was preserved in patients receiving anesthesia with propofol-remifentanil compared with sevoflurane (17). However, another study investigating the dose-dependent effects of remifentanil on regional cerebral blood flow (rCBF) measured using PET in volunteers showed significant increases in relative rCBF in the lateral prefrontal cortices at a dose of 0.05 μg/kg/min, whereas rCBF was decreased in the basal mediofrontal cortex, cerebellum, superior temporal lobe, and midbrain gray matter. In contrast, remifentanil at a higher dose of 0.15 μg/kg/min increased the rCBF in the mediofrontal and anterior cingulate cortices, occipital lobe transition and caudal periventricular gray matter (18). Therefore, the

lower dose of remifentanil administered to the GA+PVB group might have influenced the local balance of the oxygen supply and demand in the PFC, since there were no systemic hemodynamic changes in the sBP or heart rate (Table 4). Because the PFC shares multiple common connections with pain-processing brain areas, further investigation is required to evaluate how analgesics including opioids influence on local oxygenation in the PFC under general anesthesia.

In this study, monitoring was performed for only 3 min before and after the incision at the start of surgery, and the influence of amplification or modulation of nociceptive signals according to the surgical procedure was not investigated. However, Derbyshire *et al.* demonstrated that reduced rCBF was detected by PET in the left medial-dorsolateral prefrontal area (BA9) and orbito-frontal area (BA32) in response to the experimental heat pain in patients undergoing surgical removal of left-sided wisdom teeth compared with the control group, whereas the right thalamus and S1 were activated (19). These data suggest that these frontal areas are suppressed by acute nociceptive processing in the presence of ongoing acute inflammation, while nociceptive signals are transmitted to the thalamus and S1 contralateral to the heat-stimulated sites. Therefore, intraoperative nociception can induce both an increase and decrease in cerebral blood flow in the prefrontal area, which may depend on the progression of the surgical procedure and the development of inflammation. In addition, monitoring by NIRS at multiple sites including the area corresponding to the somatosensory cortex, might be required to evaluate the presence or absence of intraoperative pain.

Changes in the BIS were also monitored to evaluate asymmetry of the hemispheres and compare them with the changes in rCBF. The bilateral BIS were significantly decreased on both sides 1 min after the start of surgery in the GA group (Fig. 5a), but not in the GA+PVB group (Fig. 5b). An increase in large delta wave activity in the frontal areas of the brain is reportedly often induced by surgical incision, resulting in decreased BIS values (20, 21). However, it is unclear whether unilateral changes in BIS can be observed by incision. The possibility that the doses of remifentanil might have a complete analgesic effect on incision-induced nociception cannot be excluded.

A limitation of our study is that the analgesic levels of the PVB at the start of surgery and the influence of 1% mepivacaine injected through the epidural catheter before the induction of anesthesia are not clear. In addition, the baseline hemodynamic observations were recorded at the time of lateral decubitus positioning. Therefore, the influence of the lateral decubitus position on our findings cannot be excluded.

In conclusion, both ΔO_2Hb and ΔtotalHb increased in the contralateral frontal area in response to skin incision made under general anesthesia, an effect that was nullified by PVB. NIRS may be a useful for evaluating the depth of analgesia under general anesthesia.

References

1. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain. 2005;9(4):463-84.

2. Hsieh JC, Belfrage M, Stone-Elander S, Hansson P, Ingvar M. Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. Pain. 1995;63(2):225-36.

3. Lorenz J, Cross DJ, Minoshima S, Morrow TJ, Paulson PE, Casey KL. A unique representation of heat allodynia in the human brain. Neuron. 2002;35(2):383-93.

4. Hsieh JC, Stahle-Backdahl M, Hagermark O, Stone-Elander S, Rosenquist G, Ingvar M. Traumatic nociceptive pain activates the hypothalamus and the periaqueductal gray: a positron emission tomography study. Pain. 1996;64(2):303-14.

5. Rosen SD, Paulesu E, Nihoyannopoulos P, Tousoulis D, Frackowiak RS, Frith CD, et al. Silent ischemia as a central problem: regional brain activation

compared in silent and painful myocardial ischemia. Ann Intern Med. 1996;124(11):939-49.

6. Silverman DH, Munakata JA, Ennes H, Mandelkern MA, Hoh CK, Mayer EA. Regional cerebral activity in normal and pathological perception of visceral pain. Gastroenterology. 1997;112(1):64-72.

7. Pogatzki-Zahn EM, Wagner C, Meinhardt-Renner A, Burgmer M, Beste C, Zahn PK, et al. Coding of incisional pain in the brain: a functional magnetic resonance imaging study in human volunteers. Anesthesiology. 2010;112(2):406-17.

8. Muthalib M, Re R, Zucchelli L, Perrey S, Contini D, Caffini M, et al. Effects of Increasing Neuromuscular Electrical Stimulation Current Intensity on Cortical Sensorimotor Network Activation: A Time Domain fNIRS Study. PLoS One. 2015;10(7):e0131951.

9. Yennu A, Tian F, Gatchel RJ, Liu H. Prefrontal hemodynamic mapping by functional near-infrared spectroscopy in response to thermal stimulations over three body sites. Neurophotonics. 2016;3(4):045008.

10. Becerra L, Aasted CM, Boas DA, George E, Yucel MA, Kussman BD, et al. Brain measures of nociception using near-infrared spectroscopy in patients undergoing routine screening colonoscopy. Pain. 2016;157(4):840-8.

11. Kussman BD, Aasted CM, Yucel MA, Steele SC, Alexander ME, Boas DA, et al. Capturing Pain in the Cortex during General Anesthesia: Near Infrared Spectroscopy Measures in Patients Undergoing Catheter Ablation of Arrhythmias. PLoS One. 2016;11(7):e0158975.

12. Lee CH, Sugiyama T, Kataoka A, Kudo A, Fujino F, Chen YW, et al. Analysis for distinctive activation patterns of pain and itchy in the human brain cortex measured using near infrared spectroscopy (NIRS). PLoS One. 2013;8(10):e75360.

13. Yucel MA, Aasted CM, Petkov MP, Borsook D, Boas DA, Becerra L. Specificity of hemodynamic brain responses to painful stimuli: a functional near-infrared spectroscopy study. Sci Rep. 2015;5:9469.

14. Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, et al. Chronic pain and the emotional brain: specific brain activity associated with

spontaneous fluctuations of intensity of chronic back pain. J Neurosci. 2006;26(47):12165-73.

15. Ji G, Neugebauer V. Pain-related deactivation of medial prefrontal cortical neurons involves mGluR1 and GABA(A) receptors. J Neurophysiol. 2011;106(5):2642-52.

16. Meyer K. The role of dendritic signaling in the anesthetic suppression of consciousness. Anesthesiology. 2015;122(6):1415-31.

17. Conti A, Iacopino DG, Fodale V, Micalizzi S, Penna O, Santamaria LB. Cerebral haemodynamic changes during propofol-remifentanil or sevoflurane anaesthesia: transcranial Doppler study under bispectral index monitoring. Br J Anaesth. 2006;97(3):333-9.

18. Wagner KJ, Willoch F, Kochs EF, Siessmeier T, Tolle TR, Schwaiger M, et al. Dose-dependent regional cerebral blood flow changes during remifentanil infusion in humans: a positron emission tomography study. Anesthesiology. 2001;94(5):732-9.

19. Derbyshire SW, Jones AK, Collins M, Feinmann C, Harris M. Cerebral

responses to pain in patients suffering acute post-dental extraction pain measured by positron emission tomography (PET). Eur J Pain. 1999;3(2):103-13.

20. Morimoto Y, Matsumoto A, Koizumi Y, Gohara T, Sakabe T, Hagihira S. Changes in the bispectral index during intraabdominal irrigation in patients anesthetized with nitrous oxide and sevoflurane. Anesth Analg. 2005;100(5):1370-4, table of contents.

21. Zbinden AM, Maggiorini M, Petersen-Felix S, Lauber R, Thomson DA, Minder CE. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. I. Motor reactions. Anesthesiology. 1994;80(2):253-60.

Figure legends

Fig. 1, a) Changes in oxygenated hemoglobin (ΔO_2Hb) in the ipsilateral and contralateral frontal areas upon thoracotomy incision in patients receiving only general anesthesia **(**GA). **P* < 0.05, ***P* < 0.01 between ipsilateral and contralateral hemispheres; †*P* <0.05, ††*P* < 0.01 compared with ΔO_2Hb in the contralateral hemisphere 1 min before incision. **b**) ΔO_2Hb in patients receiving GA with a paravertebral block (GA+PVB), §§*P* <0.01 compared with ΔO_2Hb 1 min before incision in the ipsilateral hemisphere. †† *P* < 0.01 compared with ΔO_2Hb 1 min before incision in the contralateral hemisphere. Time points: *-1 min*, 1 min before incision; *start of surgery*, at the time of incision; *+1 min*, 1 min after incision; *+2min*, 2 min after incision. The values shown at each time point are the difference from baseline, measured 2 min before the incision. Abbreviations: ipsi, ipsilateral hemisphere in relation to surgery side; contra, contralateral hemisphere in relation to surgery side.

Fig. 2, a) Changes in deoxygenated hemoglobin (Δ HHb) in the ipsilateral and contralateral frontal areas upon thoracotomy incision in patients receiving only general anesthesia **(**GA). †*P* < 0.05, ††*P* < 0.01 compared with Δ HHb in the contralateral hemisphere 1 min before incision. **b)** Δ HHb in patients receiving GA with a paravertebral block (GA+PVB). §§*P* < 0.01 compared with ΔHHb in the ipsilateral hemisphere 1 min before incision. ††*P* <0.01 compared with Δ HHb in the contralateral

hemisphere 1 min before incision. Time points: *-1 min*, 1 min before incision; *start of surgery*, at the time of incision; *+1 min*, 1 min after incision; *+2 min*, 2 min after incision. The values shown at each time point are the difference from baseline, measured 2 min before the incision. Abbreviations: ipsi, ipsilateral hemisphere in relation to surgery side; contra, contralateral hemisphere in relation to surgery side.

Fig. 3, a) Changes in total hemoglobin (Δ totalHb) in the ipsilateral and contralateral frontal areas upon thoracotomy incision in patients receiving only general anesthesia **(**GA). **P* < 0.05 between ipsilateral and contralateral hemispheres, ††*P* <0.01 compared with Δ total Hb in the contralateral hemisphere at 1min before incision. **b)** Δ totalHb in patients receiving GA with a paravertebral block (GA+PVB). Time points: *-1 min*, 1 min before incision; *start of surgery*, at the time of incision; *+1 min*, 1 min after incision; *+2min*, 2 min after incision. The values shown at each time point are the difference from baseline, measured 2 min before the incision. Abbreviations: ipsi, ipsilateral hemisphere in relation to surgery side; contra, contralateral hemisphere t in relation to surgery side.

Fig. 4, a) Changes in tissue oxygen index (Δ TOI) in the ipsilateral and contralateral frontal areas upon thoracotomy incision in patients receiving only general anesthesia **(**GA). **b)** Δ TOI in patients receiving GA and paravertebral block (GA+PVB). ††*P* <

0.01 compared with Δ TOI in the ipsilateral hemisphere 1 min before incision, §§*P* < 0.01 compared with Δ TOI in the contralateral hemisphere 1 min before incision. Time points: *-1 min*, 1 min before incision; *start of surgery*, at the time of incision; *+1 min*, 1 min after incision; *+2 min*, 2 min after incision. The values shown at each time point are the difference from baseline, measured 2 min before the incision. Abbreviations: ipsi, ipsilateral hemisphere in relation to surgery side; contra, contralateral hemisphere in relation to surgery side.

Fig. 5: a) Changes in bilateral bispectral index (BIS) in the ipsilateral and contralateral frontal areas upon thoracotomy incision in patients receiving only general anesthesia **(**GA). **b)** Changes in BIS in patients receiving GA with a paravertebral block (GA+PVB). ††*P* <0.01 compared with BIS in the ipsilateral hemisphere 1 min before incision, §*P* < 0.05, §§*P* < 0.01 compared with BIS in the contralateral hemisphere 1min before incision. Time points: *-1 min*, 1 min before incision; *start of surgery*, at the time of incision; *+1 min*, 1 min after incision; *+2min*, 2 min after incision. The values shown at each time point are the difference from baseline, measured 2 min before the incision. Abbreviations: ipsi, ipsilateral hemisphere in relation to surgery side; contra, contralateral hemisphere in relation to surgery side.

Table 1 demographic and clinical characteristics of patients.

	GA (n = 17)	GA + PVB (n = 17)	*P* value
Sex (male / female)	11 / 6	10 / 7	0.72
Age (y)	61 ± 15	66 ± 10	0.13
Height (cm)	160 ± 10	160 ± 9	0.94
Weight (kg)	59 ± 8	62 ± 11	0.63
ASA physical status score I / II	4 / 13	0 / 17	0.1
Hemoglobin (g / dl)	12.2 ± 1.2	11.6 ± 1.3	0.22

ASA: American Society of Anesthesiologists, GA: General Anesthesia, PVB: Paravertebral Block

Table 2 Comparison of physiological variables between the two groups

	GA	GA + PVB	*P* value
pH	7.35 ± 0.04	7.36 ± 0.05	0.34
PaO2 (mmHg)	143 ± 55	152 ± 82	0.966
PaCO2 (mmHg)	48 ± 5	45 ± 5	0.14
Hb (g / dl)	12.1 ± 1.7	11.5 ± 1.4	0.23

Table 3 Comparison of the dose of propofol and reminentanil between the two groups

	GA	GA+PVB	*P* value
Propofol (μg/ml)	2.7 ± 0.4	2.7 ± 0.3	0.97
Remifentanil (μg/kg/min)	0.36 ± 0.1	0.29 ± 0.1	0.03

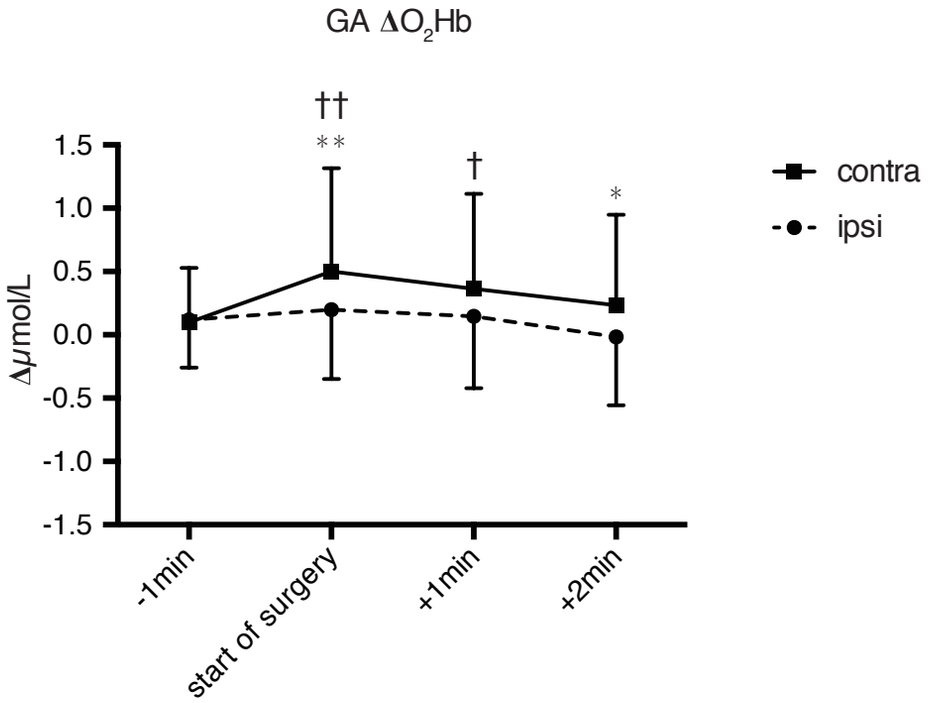
Table 4 Comparison of the hemodynamic variables between the two groups

		GA	GA + PVB	*P* value
SpO2 (%)	-1min	98 ± 2	99 ± 2	0.3457
	0	98 ± 2	98 ± 2	0.4918
	+1min	98 ± 2	98 ± 2	> 0.9999
	+2min	98 ± 2	98 ± 2	> 0.9999
Systolic BP (mmHg)	-1min	96 ± 15	107 ± 15	0.1649
	0	96 ± 15	107 ± 15	0.1148
	+1min	97 ± 15	106 ± 15	0.3148
	+2min	97 ± 14	106 ± 15	0.2781
HR (bpm)	-1min	67 ± 10	68 ± 12	> 0.9999
	0	66 ± 10	68 ± 14	> 0.9999
	+1min	66 ± 10	69 ± 14	> 0.9999
	+2min	66 ± 10	69 ± 14	> 0.9999

BP: blood pressure, HR: heart rate.

Fig. 1

a


GA ΔO2Hb
††
**
†
*
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Δμmol/L
-1min
start of surgery
+1min
+2min
contra
ipsi

b

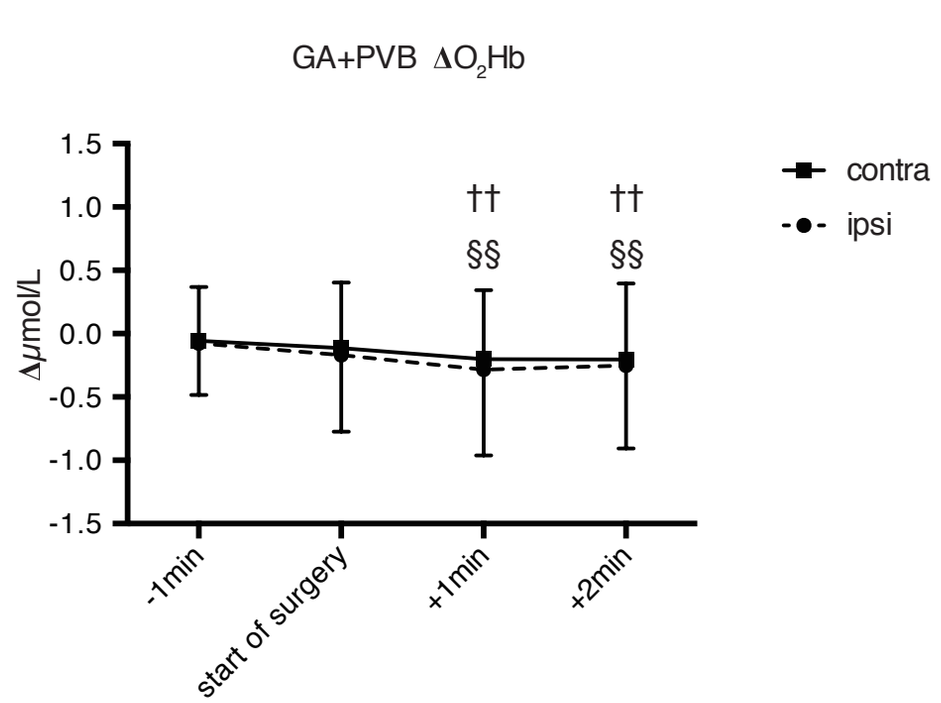
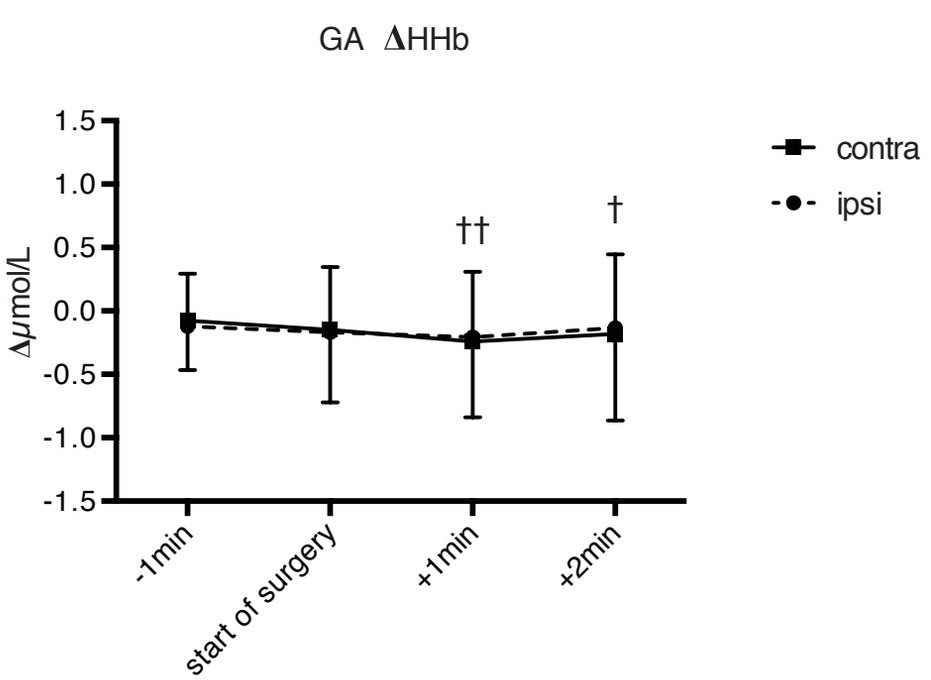

GA+PVB ΔO2Hb
††
§§
††
§§
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Δμmol/L
-1min
start of surgery
+1min
+2min
contra
ipsi

Fig. 2

a


GA ΔHHb
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Δμmol/L
††
†
-1min
start of surgery
+1min
+2min
contra
ipsi

b

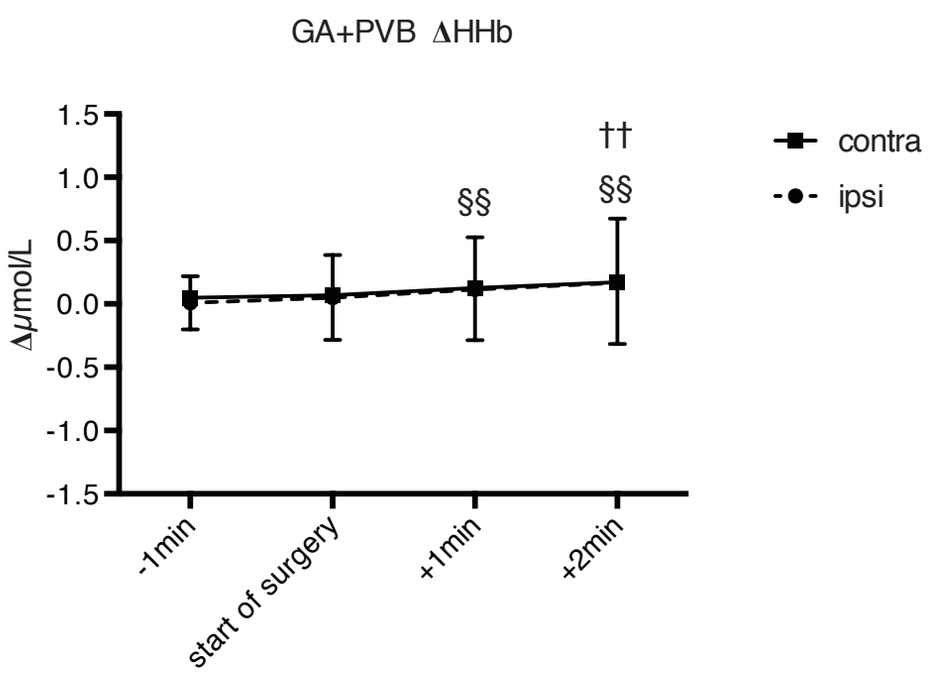

GA+PVB ΔHHb
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Δμmol/L
§§
§§
††
-1min
start of surgery
+1min
+2min
contra
ipsi

Fig. 3

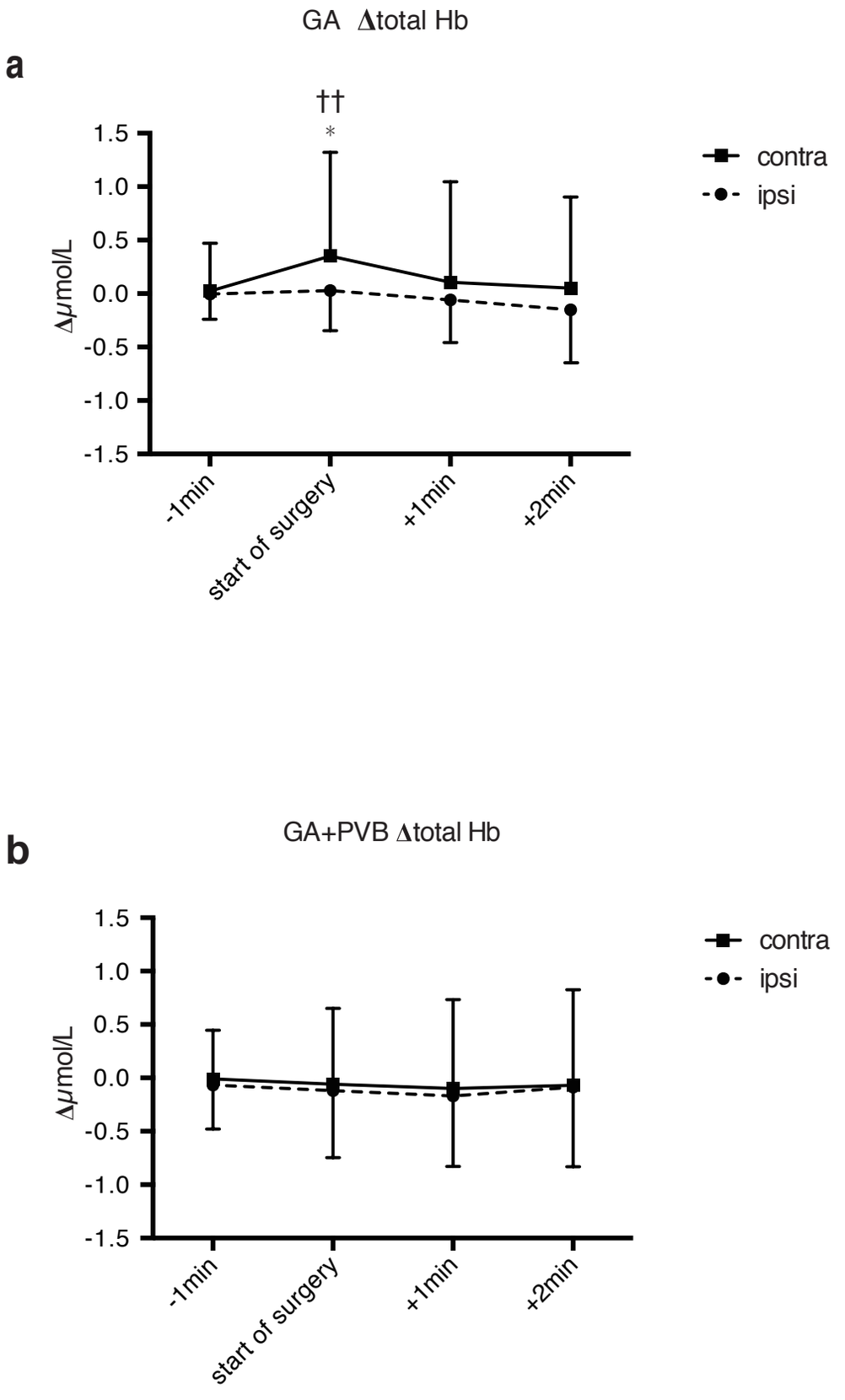

a
GA Δtotal Hb
††
*
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Δμmol/L
-1min
start of surgery
+1min
+2min
contra
ipsi
b
GA+PVB Δtotal Hb
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Δμmol/L
-1min
start of surgery
+1min
+2min
contra
ipsi

Fig. 4

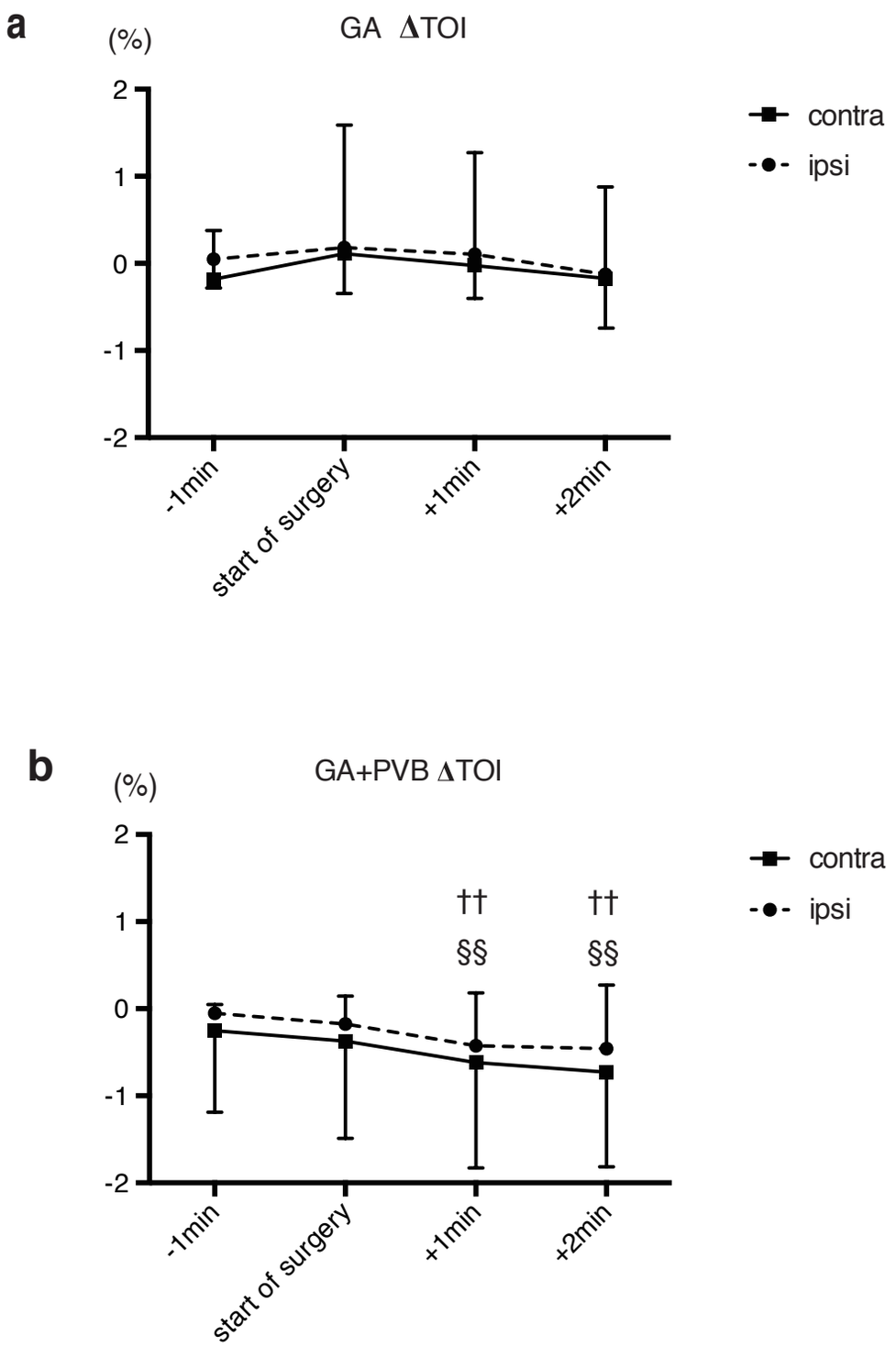
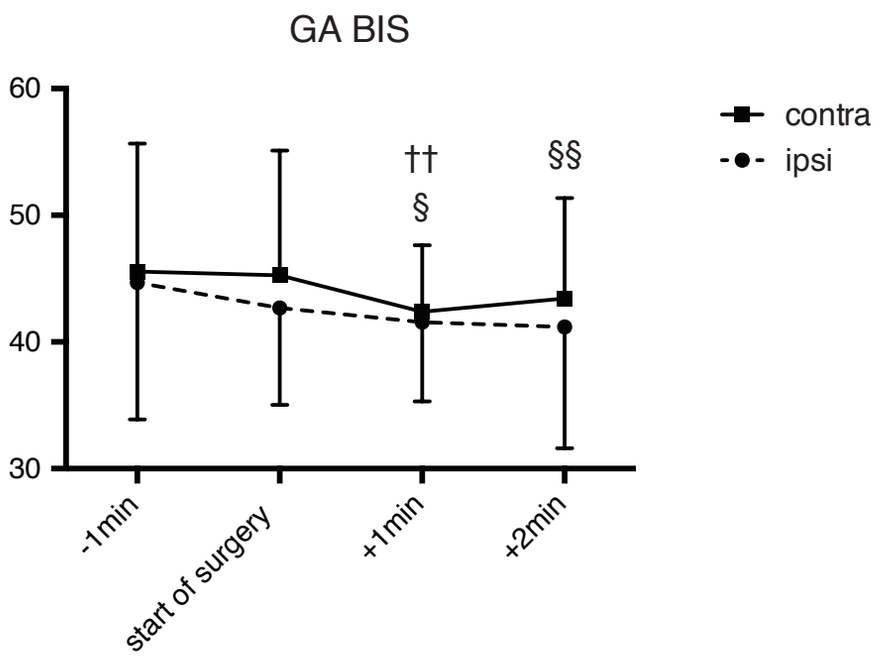
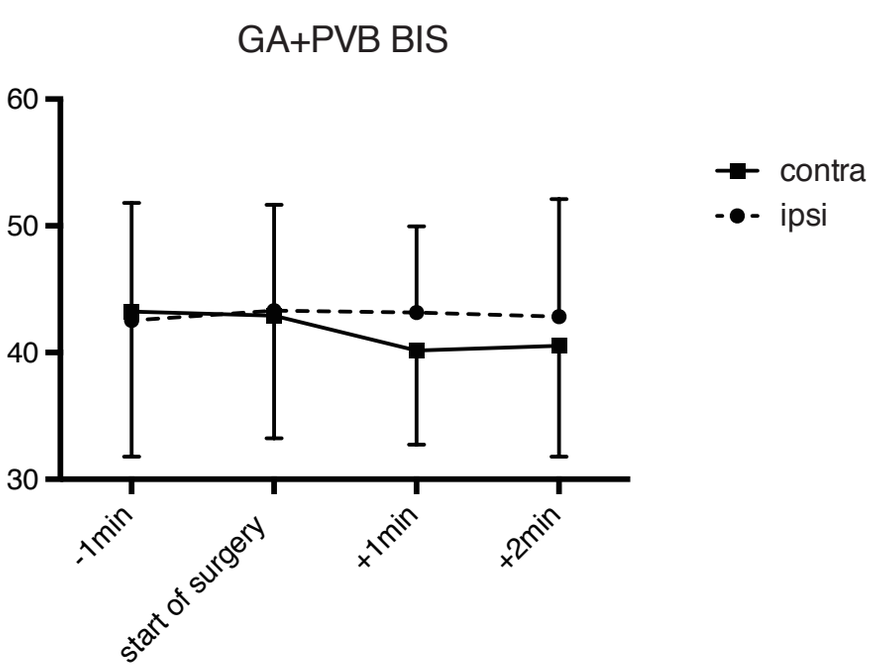

a
GA ΔTOI
(%)
2
1
0
-1
-2
-1min
start of surgery
+1min
+2min
contra
ipsi
b
GA+PVB ΔTOI
(%)
2
1
0
-1
-2
††
§§
††
§§
-1min
start of surgery
+1min
+2min
contra
ipsi

Fig. 5

a


GA BIS
60
50
40
30
††
§
§§
contra
ipsi
-1min
start of surgery
+1min
+2min

b


GA+PVB BIS
60
50
40
30
contra
ipsi
-1min
start of surgery
+1min
+2min