Anesthetic Substitute of Intraoperative Regional Anesthesia of Nonintubated or Endotracheal-intubated Video-assisted Thoracoscopic Surgery With Thoracoscopic Multilevel Intercostal Nerve Blocks: a Randomized Study

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Research

Keywords: bispectral index, Ce of propofol, Ce of remifentanil, depth of anesthesia, intercostal nerve blocks, video-assisted thoracoscopic surgery

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Abstract

Background:

A reduced need for general anesthetics and enhanced effectiveness of postoperative analgesia have been reported for multimodal anesthesia, which involves combining regional and general anesthesia. Ideal regional anesthesia to combine with general anesthesia should match but not overdo with the surgical stress from corresponding operations. However, as thoracic operation becomes less invasive, the substitute effects on intraoperative analgesia or consciousness by regional anesthesia such as with thoracoscopic intercostal nerve blocks (TINBs) for managing corresponding surgical stress in intubated or non-intubated video-assisted thoracoscopic surgery (VATS) have been inadequately studied. The goals of this study is to investigate the substitue of TINBs on analgesia and consciousness for intubated and non-intubated uniport VATS operations.

Methods:

Sixty patients who received VATS with target-controlled infusions of propofol and remifentanil were recruited. Patients were randomized into intubated and nonintubated groups. Intraoperative multilevel (T3–T8) TINBs were performed after artificial pneumothorax and before VATS operations. The effects of substitute on analgesia by TINBs for VATS operations were indicated by changes on blood pressure and the Ce of remifentanil to maintain normotension. EEG data with a density spectral array (DSA) and data on the effect-site concentration (Ce) of propofol goaled with bispectral index (BIS) levels between 40-60 were compared to determine whether TINBs affect consciousness.

Results:

TINBs with 0.5% bupivacaine provide substitute more than required on analgesia for intubated and non-intubated uniport VATS operations. The Ce of remifentanil was significantly decreased beginning 10 min after TINBs in both groups (p < 0.001). In the nonintubated VATS (NIVATS) group, a significantly lower mean arterial pressure after introducing TINBs persisted for 20 min. TINBs demonstrated a DSA smoothing effect despite the subsequent VATS. The Ce of the propofol infusion decreased 5 min after TINBs in both NIVATS (p < 0.001) and intubated VATS (IVATS; p = 0.252) groups. The Ce of remifentanil was significantly higher in parallel for the IVATS group than for the NIVATS group (p < 0.001).

Conclusions:

Intraoperative TINBs with 0.5 % bupivacaine provides substitutes on analgesia and hyponosis more than required for uniportal intubated or non-intubated VATS operations. Situations involving endotracheal tubes required more analgesia but does not affect the substitute effects of TINBs.

Trial registration:

ClinicalTrials. gov, NCT03874403.
This study was approved by the Research Ethics Committee of National Taiwan University Hospital, Taipei, Taiwan (201712125RINB) on February 2, 2018. We then enrolled our first case on November 1, 2018 - Retrospective registered on February 28, 2019, https://clinicaltrials.gov/ct2/show/record/NCT03874403

**Background**

Combining regional blocks onto general anesthesia has become popular because it involves a lower intraoperative requirement for anesthetics, fewer adverse effects from general anesthesia, and superior postoperative analgesia (1, 2). The ideal regional anesthesia to combine with general anesthesia is to provide anesthesia matching with the surgical stress from the corresponding operations without frequent adjustment of general anesthesia or managements of unwanted hypotension. However, too deep anesthesia following regional anesthesia is not uncommon because regional anesthesia could possibly overdo with the corresponding surgical stress. Despite reducing general anesthetics, hypotension after thoracic epidural anesthesia (3, 4) and intercostal nerve blocks (5) for thoracic operations is usually managed with more intravenous fluid infusion or vasoactive agents (6, 7). Reducing the regimen for local anesthetics has also been recommended to prevent hypotensive episodes with thoracic epidural anesthesia (3, 4).

However, as thoracic operations become less and less invasive, a gap of knowledge about the perioperative analgesia required for thoracic operations has been noticed (8, 9). Instead of the conventional thoracic epidural anesthesia, perioperative regional anesthesia such as intercostal nerve blocks (10), erector spine plane block (2), or paravertebral blockade (11), has become favored (12–14). However, with the rapid progress on minimization of anesthetic and surgical stimulation (15, 16) for video-assisted thoracoscopic surgery (VATS), the gold standards for the optimal intraoperative regional anesthesia applied for VATS has not been concluded (17).

The art of combining regional anesthesia on general anesthesia is goaled to provide the optimal anesthetic depth preventing switch-on the memory, consciousness, noxious arousal systems and the somatic and postoperative analgesic responses to the corresponding surgical stimulation (18). Profound degrees of hypnosis in the absence of analgesia will not prevent the hemodynamic responses to profoundly noxious stimuli. Also, profound degrees of analgesia do not guarantee unconsciousness. As combination of hypnosis and analgesia suppresses hemodynamic response to noxious stimuli and guarantees unconsciousness (19), the substitute of regional anesthesia on hypnosis and analgesia has not been fully understood.

Although regional anesthesia was reported to prevent an increase in noxious response with limited hemodynamic changes after initiating VATS (20), questions remain to be answered on how much will the analgesia could be provided by different regional anesthesia (14, 21, 22) for different corresponding VATS operations.
By reducing the afferent input from thoracic cage (23), regional anesthesia such as thoracoscopic intercostal nerve blocks (TINBs) may also provide anesthesia on hypnosis component. In our retrospective study on nonintubated VATS (NIVATS), TINBs was shown to decrease the effect-site concentration (Ce) of propofol infusions with bispectral index (BIS)-guided sedation (24). Nowadays, electroencephalography (EEG) monitors (25–30) were reported effective tools to investigate how regional anesthesia affects consciousness. The noxious stimulation with existing endotracheal tubes has not been elucidated although VATS operations have been performed either intubated or non-intubated.

In this study, the substitute of regional anesthesia to the corresponding VATS operations was analyzed with the model by TINBs performed by surgeon through the first thoracoscopic port immediately before VATS. The changes on EEG monitoring and the requirement of propofol infusion for maintaining BIS levels between 40–60 were used to analyze the substitute of TINBs to maintain optimal consciousness. The changes on hemodynamics (20, 31–33) and Ce of remifentanil to subsequently corresponding VATS operation were used to determine the substitute of TINBs for analgesia. Intubated VATS (IVATS) and NIVATS patients were included to determine if the existing endotracheal tubes affect the substitute by TINBs on hypnosis or analgesia.

**Methods**

**Patients**

Ethical approval for the study (201712125RINB) was granted by the Research Ethics Committee (Chairperson Professor Fu-Chang Tsai) of National Taiwan University Hospital, Taipei, Taiwan, on February 2, 2018, and the study was registered at http://clinicaltrials.gov with the identifier NCT03874403. Patients who were scheduled for uniport thoracoscopic surgery and lung isolation and who were determined suitable candidates for NIVATS were recruited. Patients were excluded if they had significant renal or hepatic diseases or abnormal cardiopulmonary function, including heart failure categorized beyond class II of the New York Heart Association Functional Classification, chronic obstructive pulmonary disease, or active coronary arterial disease.

**Randomization and group assignments**

We obtained written informed consent from all patients the day before their surgeries. Upon patients’ arrival at the operating theater, we randomly assigned the patients by using computer-generated random numbers, which were enclosed in sequentially numbered, sealed envelopes. Patient confidentiality was ensured by the research assistant, who was unaware of the patients’ characteristics and was not responsible for clinical work. The envelope was checked immediately before anesthesia induction.

**Anesthetic management**

Pulse oximetry, electrocardiography, blood pressure, bilateral frontal BIS (BIS Quatro, Aspect Medical System, Norwood, MA, USA) with density spectral array (DSA), and end-tidal carbon dioxide (ETCO₂)
concentration were used for intraoperative monitoring. After the baseline data were recorded, anesthesia was induced and maintained in both groups with a target-controlled infusion of intravenous propofol and remifentanil (Injectomat TIVA Agilia, Fresenius Kabi GmbH, Graz, Austria). An arterial catheter was inserted for hemodynamic monitoring and arterial blood gas analysis in both groups. In the IVATS group, 1 mg/kg rocuronium was administered after anesthesia induction to facilitate endotracheal tube insertion. The ventilation was set to a tidal volume of 6–8 mL/kg during two-lung ventilation and 3–4 mL/kg during one-lung ventilation, with an ETCO$_2$ target of 40 mmHg. In the NIVATS group, spontaneous breathing was smoothly maintained with a respiratory rate between 12 and 18 breaths per minute by adjusting propofol and remifentanil infusion with a transnasal humidified rapid-insufflation ventilator exchange (34). The propofol target Ce level was titrated to maintain a BIS of 40 to 60 throughout the surgeries. The remifentanil target in the NIVATS group was adjusted in response to systemic blood pressure during anesthesia maintenance to ensure mean arterial pressure (MAP) remained within 20% of the baseline and to ensure the respiratory rate remained at 12–18 breaths/minute. A vasoactive agent such as ephedrine or norepinephrine was administered as an intravenous bolus if the change in MAP was a $>30\%$ difference from the baseline after adjusting for the remifentanil infusion. With similar goals on hemodynamic variables and BIS scores, the Ce levels of both remifentanil and propofol were recorded and analyzed along with subsequent uniport VATS.

**Intraoperative TINBs**

Once patients were in the decubitus position and surgical preparations had been completed with BIS scores maintained at a range of 40–60, the first thoracoscopic port was placed after local infiltration of 2 mL of 2% lidocaine to induce artificial pneumothorax (AP). Subsequently, TINB was produced through infiltration of 0.5% bupivacaine (1.5 mL for each intercostal space) from T3 to T8 through the first thoracoscopic port (13). The period from AP to TINB completion was calculated as the TINB time. After TINB completion, thoracoscopic vagal nerve blocks were administered in patients in the NIVATS group, but not to those in the IVATS group, to prevent accidental cough.

**Operations and recovery**

VATS was begun immediately for both groups after nerve block completion. After the surgical procedures were completed, pigtail catheters were inserted. Patients were sent to the post-anesthetic care unit (PACU) or the intensive care unit (ICU) after extubation when BIS was $>85$. Additional intravenous morphine was administered until patients reported a pain score $<3$ on a numerical rating scale in the PACU.

**Data collection**

BIS and density spectral array (DSA) records were obtained from the output of a bilateral frontal BIS sensor (BIS Quatro, Aspect Medical System, Norwood, MA, USA). Intraoperative hemodynamic variables, including arterial blood pressure, heart rate (HR), Ce levels under propofol and remifentanil infusions, and the use of vasoconstrictors, were collected from anesthetic records. Clinical data, including length of
hospital and ICU stays and any cardiac, pulmonary, or other major organ complications, were collected through chart review. All data were prospectively collected and retrospectively analyzed.

To determine the sequential effects of TINBs on consciousness and analgesia, monitored data and the Ce for each drug were compared at sequential timepoints, including the preoperative baseline, AP initiation, TINB completion, start of surgical procedures, and subsequent 5-min intervals.

**Statistical analysis**

A pilot study determined that the Ce of propofol decreased by 0.4 on average with a standard deviation of 0.7; the Ce of remifentanil decreased by 0.18 on average with a 0.31 standard deviation after the use of TINBs. Using Sigmaplot (version 13; Systat Software, USA) statistical software, we estimated that a sample size of 27 patients to study changes of propofol and 26 patients to study changes of remifentanil would provide 80% power with an alpha level of 0.05. We therefore enrolled 30 patients per group.

The results were statistically analyzed using Sigmaplot, and \( p \) values < 0.05 were considered statistically significant. Findings are presented as mean ± standard deviation unless otherwise specified. Findings based on categorical data were tested using Fisher’s exact test; otherwise, the independent Student’s \( t \) test was used. A one-way analysis of variance (ANOVA) was used to compare variables with timepoints from the start of the surgical procedure up to 50 min after TINBs in either the NIVATS or IVATS group. A two-way ANOVA was applied to evaluate the time effect, group effect, and interaction between the two factors.

**Results**

Sixty patients participated in this study from November 1, 2018, to October 2, 2019. In the IVATS group, left-sided double-lumen tubes were inserted in three patients, and rigid-angled uniblockers (Coopdech Endobronchial Blocker Tube, Daiken Medical) were inserted through 8.0-mm ID endotracheal tubes in the other 27 patients. The patients in both groups exhibited comparable baseline characteristics (Table 1).
Table 1
Patient characteristics

|                        | NIVATS (*n* = 30) | IVATS (*n* = 30) | *P* value |
|------------------------|-------------------|------------------|-----------|
| Age, yr                | 54.7 ± 6.7        | 54.6 ± 6.7       | 0.461     |
| Female, no (%)         | 19 (63)           | 23 (77)          | 1         |
| Height, cm             | 157.3 ± 7.6       | 161.6 ± 8.3      | 0.151     |
| Weight, kg             | 56.8 ± 8.7        | 60.3 ± 10.1      | 0.083     |
| Preoperative pulmonary function test |          |                  |           |
| FVC (%)                | 113.2 ± 15.5      | 108.3 ± 9.9      | 0.176     |
| FEV1 (%)               | 111.9 ± 16.5      | 107 ± 10         | 0.403     |
| History of smoking, (n; %) | 1              | 0               | 0.336     |
| Coexisting disease, n  |                  |                  |           |
| Hypertension, n        | 8 (27%)           | 5 (17%)          | 0.3       |
| Diabetes mellitus, n   | 3 (10%)           | 5 (17%)          | 1         |
| Asthma, n              | 1 (3%)            | 1 (3%)           | 1         |
| ASA classification score (n; %) |      |                  |           |
| I                      | 13 (43%)          | 7 (23%)          | 0.10      |
| II                     | 17 (57%)          | 22 (73%)         | 0.19      |
| III                    | 0 (0%)            | 1 (3%)           | 0.34      |

FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; ASA = American Society of Anesthesiologists

Operative profiles and clinical outcomes

Table 2 presents the operative data. All patients except one in the NIVATS group received complete uniport VATS. BIS scores were near 40 at the start of the surgical procedures with AP. When AP was used, the Ce of propofol was slightly but nonsignificantly higher in the NIVATS group, whereas the Ce of remifentanil was significantly lower in the NIVATS group (*p* = 0.049), with mean arterial pressure (MAP) significantly lower than that in the IVATS group (*p* = 0.001).
Table 2
Operation profiles

|                                | NIVATS (n=30) | IVATS (n=30) | P    |
|--------------------------------|---------------|--------------|------|
| **Baseline data**              |               |              |      |
| MAP (mmHg)                     | 103.7 ± 12.5  | 105.0 ± 17.1 | 0.37 |
| HR (beats/min.)                | 76.9 ± 13.1   | 77.2 ± 11.1  | 0.462|
| **Intraoperative Vasoconstrictor** |            |              |      |
| Ephedrine administration (N)   | 1             | 0            | 1.00 |
| **Data at time at AP (start of operations)** |            |              |      |
| BIS level                      | 43.9 ± 9.5    | 40.0 ± 7.3   | 0.08 |
| Ce of propofol                 | 3.28 ± 0.65   | 2.95 ± 0.96  | 0.078|
| Ce of remifentanil             | 0.59 ± 0.31   | 0.91 ± 0.65  | 0.049*|
| **Procedure time (minutes)**   |               |              |      |
| Anaesthesia time               | 100.3 ± 33.0  | 95.0 ± 34.4  | 0.333|
| TINB time                      | 4.5 ± 2.1     | 3.3 ± 1.0    | 0.015*|
| Operation time                 | 74.3 ± 33.1   | 68.8 ± 32.7  | 0.387|
| Lowest SpO2 (%) during OLV     | 97.3 ± 2.3    | 97.9 ± 2.0   | 0.321|
| **Operations (n; %)**          |               |              |      |
| Left VATS                      | 9 (30%)       | 9 (30%)      | 1    |
| Uniportal lobectomy            | 3 (10%)       | 3 (10%)      | 1    |
| Uniportal segmentectomy        | 3 (10%)       | 3 (10%)      | 1    |
| Uniportal wedge resection      | 3 (10%)       | 3 (10%)      | 1    |
| Right VATS                     | 21 (70%)      | 21 (70%)     | 1    |
| Uniportal lobectomy            | 6 (20%)       | 3 (10%)      | 0.28 |
| Biportal lobectomy             | 1 (3.3%)      | 0 (0%)       | 0.32 |
| Uniportal segmentectomy        | 1 (3.3%)      | 3 (10%)      | 0.30 |
| Uniportal wedge resection      | 13 (43%)      | 15 (50%)     | 0.59 |

Data are expressed as mean ± standard deviation. * significantly different between groups.

TINB time: from artificial pneumothorax to completion of TINBs from T3 to T8
MAP = mean arterial pressure; HR = heart rate
Table 3 presents the postoperative outcomes. All patients in the IVATS group were extubated and sent to the PACU. All patients in the NIVATS group were sent to the PACU except one who stayed in the ICU for 12 h. The postoperative outcomes nonsignificantly differed between the two groups.

Table 3

| Postoperative outcomes | NIVATS (n=30) | IVATS (n=30) | P |
|------------------------|--------------|--------------|---|
| Hospitalization        |              |              |   |
| ICU stay (n, %)        | 1 (3.3%)     | 0 (0%)       | 0.32 |
| Hospitalization (days) | 4 ± 2.3      | 3.5 ± 1.1    | 0.92 |
| Removal of pigtails (days) | 2.2 ± 2.2 | 1.9 ± 1.4    | 0.99 |
| Pain scale             |              |              |   |
| NRS on POD1 (median ± SD) | 2 ± 1.15 | 1 ± 1.45     | 0.68 |
| Complications (n; %)   |              |              |   |
| Pneumonia              | 3 (10%)      | 1 (3.3%)     | 0.30 |
| Empyema                | 0 (0%)       | 1 (3.3%)     | 0.32 |
| Postoperative adverse effects (n; %) | | | |
| Sore throat            | 5 (17%)      | 4 (13%)      | p = 0.68 |
| Headache               | 0 (0%)       | 1 (3.3%)     | p = 0.32 |
| Nausea                 | 3 (10%)      | 3 (10%)      | p = 1.0 |
| Vomiting               | 5 (17%)      | 6 (20%)      | p = 0.77 |
| Urination difficulty   | 0 (0%)       | 1 (3.3%)     | p = 0.32 |

NRS = numerical rating scale

To investigate the effects of TINBs with variable operative periods, data were presented and compared up to 50 min after the TINBs were completely administered and surgical procedures had been completely performed.

TINB substitution of required analgesia for subsequent VATS operations

Figure 1-a presents the trends of intraoperative MAP in both groups. MAP was significantly lower in the NIVATS group (68.3 ± 9.0 mmHg) than in the IVATS group (79.9 ± 15.5 mmHg) starting from the AP timepoint (p = 0.001), despite the significantly lower Ce of the remifentanil infusion. In the IVATS group, MAP remained well within 20% of the baseline without vasoactive drugs, and the Ce of remifentanil and
propofol infusion decreased. In the NIVATS group, MAP was significantly lower than baseline at the AP timepoint without vasoactive drug management. MAP started to decrease after completion of TINBs, reaching the lowest MAP (75 ± 14% of baseline) from 5–10 min after TINBs without vasoactive drugs administration. MAP was significantly lower in the NIVATS group from AP to 20 min after TINBs. Figure 1-b illustrates the changes in the Ce of the remifentanil infusion. Between 5 min and at least 50 min, the Ce of remifentanil decreased significantly compared with that of TINBs in the NIVATS ($p < 0.001$) and the IVATS ($p = 0.014$) groups. The reductions of Ce from the AP timepoint to 20 min after TINBs were $0.25 \pm 0.44$ and $0.21 \pm 0.68$ ng/mL in the NIVATS and IVATS groups, respectively ($p = 0.94$). The trends of intraoperative HR are presented in Fig. 1-c. HR increased slightly but significantly in the NIVATS group through one-way ANOVA ($p < 0.001$), whereas it increased nonsignificantly in the IVATS group.

**Substitution from TINBs with optimal consciousness levels for VATS**

Figure 1-d illustrates the trends of BIS scores. BIS scores were near 40 and comparable at the AP timepoint in both groups. After the introduction of TINBs, BIS scores decreased nonsignificantly; they were maintained in the range of 40–60 after TINBs but remained at higher levels after stabilization. Figure 2 demonstrates DSA changes in patients from both groups. Burst suppression was exhibited in both groups after TINBs. DSA stabilized after TINBs, with gradual recovery from suppression occurring alongside decreases in propofol and remifentanil infusions despite surgical stimulation.

As Fig. 1-e demonstrates, the Ce of propofol decreased with well-maintained BIS scores in both groups. Ce of propofol significantly decreased starting at 5 min after the completion of TINBs in the NIVATS group ($p < 0.001$). Ce of propofol decreased non-significantly in the IVATS group ($p = 0.252$).

**Comparison of the effects of TINBs between the NIVATS and IVATS groups**

Table 4 indicates that the changes of BIS scores were comparable between the groups. The changes in MAP significantly differed between timepoints. The NIVATS group exhibited a significantly greater decrease in MAP. The changes in the Ce of the propofol infusion significantly decreased after TINBs but did not significantly differ between the NIVATS and IVATS groups. Moreover, the Ce of the remifentanil infusion was significantly higher in the IVATS group than in the NIVATS group at each timepoint (Fig. 1-b).
Table 4
Two-way ANOVA results on the trends of BIS, Ce of propofol, and Ce of remifentanil between the NIVATS and VATS groups at different timepoints (from AP to 50 minutes after TINBs)

| Component of anaesthesia parameters | Between groups | Within time points | Group X time |
|-------------------------------------|----------------|-------------------|--------------|
| Consciousness                       |                |                   |              |
| BIS                                 | P = 0.102      | P < 0.001*        | P = 0.334    |
| Ce of propofol                      | P = 0.23       | P < 0.001*        | P = 0.293    |
| Analgesia                           |                |                   |              |
| MAP                                 | P < 0.001*     | P < 0.001*        | P < 0.001*   |
| HR                                  | P = 0.309      | P = 0.005*        | P = 0.480    |
| Ce of remifentanil                  | P < 0.001*     | P < 0.001*        | P = 0.937    |

Group X time: the interaction between groups and time points. Data were analyzed from immediately before the operation to 50 minutes after the completion of ICBs.

Discussion

In this study, we demonstrated how much intraoperative TINBs could substitute the requirement of anesthesia including on hypnosis and analgesia for corresponding uniportal VATS. Up to our knowledge, it is the first report trying to precisely analyze the part of intraoperative regional anesthesia within the multimodal anesthesia. Based on our results, multilevel TINBs with 0.5% bupivacaine provided more-than-required analgesia for subsequently corresponding uniport VATS operations. The Ce of remifentanil infusion decreased after the introduction of TINBs besides subsequently surgical stimulations. TINBs exhibited anesthesia-deepening, rather than anesthetic-sparing, effects within 5–10 min after the complete introduction of TINBs. The analgesic effects of TINBs could be roughly calculated by using approximately 0.25 ng/mL of Ce of remifentanil in addition to the analgesic requirement of uniport VATS and were maintained throughout uniport VATS operations.

The concept of anesthetic depth is to match with the need of correspondent surgeries(35). Depth of anesthesia often refers to two components to create the anesthetic state including hypnosis created with drugs such as propofol or the inhalational anesthetics and analgesia created with the opioids(36). If the regional blockade ideally match the requirement of anesthesia from corresponding operations, BIS levels and the requirement of narcotics could be kept cocontantly with comparable hemodynamics. However, oversubstitution by regional anesthesia may come out a too deep anesthesia or severe hypotension (5, 6), which is severely concerned by surgical team and an issue may affect the operative outcomes. Based on our results, the concentration of bupivacaine for multilevel TINBs may be reduced to get the perfect “depth-of-anesthesia” appropriate for the uniport VATS operations.

Our results also indicated that tracheal intubation has an unavoidably existing noxious stimulation, requiring significantly more analgesia (about 0.3 ng/mL of Ce of remifentanil) than NIVATS. Because TINBs did not block the noxious stimulation from the existing endotracheal tubes, a higher Ce levels were
required in parallel for intubated VATS despite the similar reduction of Ce of remifentanil after TINB administration. Lower blood pressure and prolonged hypotensive effects after TINBs up to 20 minutes were shown in the NIVATS group. Low preoperative Ce (0.59 ± 0.31 ng/mL) in NIVATS group and the limited volume adjusted for diluted remifentanil limit the rapid adjustment and the recovery to normotension. It also demonstrates the possible difficulty for anesthetic management on practicing non-intubated VATS. The experience from practice for intubated VATS may usually come out with a delayed response to hypotension. If the regional anesthesia for non-intubated VATS exhibits too deep of analgesia such as TINBs in our study, hypotension may be more severe and prolonged. Based on our results, a direct but not gradual reduction of 0.25 ng/mL of Ce of remifentanil is recommended immediately after TINBs for non-intubated VATS operations.

TINBs also exhibited depressive effects in the DSA analysis, confirming the deepening effects on consciousness. The suppression of EEG dynamics, reducing alpha–beta oscillation effects after TINBs, is similar to that of additional propofol injection (26) despite the subsequent surgical procedures. To maintain BIS scores > 40, the Ce of the propofol infusion had to decrease. The EEG dynamics recovered gradually with the reduction of propofol infusion, exhibiting smoother patterns. Our results agreed with those of a previous study without surgical procedures (37). With smoother DSA patterns, our results agreed with the hypothesis that TINBs reduce consciousness by decreasing the afferent input to the brain (23). Although the smoothing effects on DSA were similar in both groups, the significant decrease in the Ce of propofol was observed in the NIVATS group. For non-intubated VATS operations, hypotension after TINBs may also indicate the interaction of too deep hypnosis and analgesia.

The addition of TINBs was proven to exhibit more analgesic effects than were required for the subsequent uniportal VATS. The Ce of the remifentanil infusion in both groups decreased 5 min after TINBs were added and was maintained at < 1 ng/mL during the subsequent surgical procedures. The Ce of the remifentanil infusion was much lower than that reported in a previous study without adding regional anesthesia; in said report, if the Ce of the remifentanil infusion was lower than 2.8 ng/mL, preventing arousal during propofol anesthesia could be challenging (38). These results may also be attributable to the extremely limited surgical stimulations of the minimally invasive approach employed in this study. Our results were similar to those of a previous study that used thoracic paravertebral blocks with nociceptive response values (20).

For NIVATS, it is more challenging for anesthetic combinations to reach a balance between safety, patient comfort, and surgeon satisfaction. With comparable BIS scores, an acceptable respiratory rate, and a significantly lower Ce of remifentanil, more profound hypotension was demonstrated in the NIVATS group with TINBs. Because hyperventilation or cough were not uncommon in the NIVATS group when AP was performed, deeper anesthesia with BIS scores near 40 was preferred before performing AP. With spontaneous breathing, the duration of performing TINB was significantly longer in the NIVATS group, even though it was prolonged for only several minutes. Vigorous reduction of the depth of sedation after completion of regional anesthesia attenuated the hypotensive risk after regional anesthesia was implemented.
Although the aim was to maintain BIS scores of 40–60, our results indicated that the anesthesiologists preferred to maintain higher BIS scores once they had confirmed the adequacy of intraoperative hypnosis and analgesia with a smooth DSA. In addition to BIS levels, DSA monitoring generally provides more data for anesthesiologists to observe and enables them to monitor the recovery of EEG dynamics, which differs between individuals.

With goal-directed adjustment, MAP values were significantly lower in the NIVATS group until 20 min after the administration of TINBs. Based on our results, we recommend reducing the concentration of local anesthetics applied for TINBs for uniport VATS to prevent hypotension, especially for NIVATS in older patients or patients with vulnerability to hemodynamic instability. Regarding real-time monitoring through DSA, the amount of required drugs could be reduced once the DSA exhibits depressive effects in advance of changes on BIS levels. This demonstrates the benefits of observing DSA rather than BIS scores.

For analgesic component analysis, other monitors, such as the analgesia nociception index (ANI), instead of hemodynamic changes were reported to help optimize analgesics in general anesthesia (32). However, the ANI was demonstrated to have low sensitivity when differentiating high and low numerical rating scale scores for acute postoperative pain (39). This study indicated that unilateral vagal nerve blocks could possibly interfere with changes in HR variability, which is the main basis for ANI monitoring (32).

This study has some limitations. First, anesthetic combinations may differ within the NIVATS group because the goal of the remifentanil infusion was to maintain a respiratory rate of 12–18 breaths/min to achieve lung collapse and satisfactory operational fields. Furthermore, although a significantly lower Ce of remifentanil was measured in the NIVATS group without surgical stimulations, the Ce of remifentanil infusion was lower throughout the use of TINBs and the subsequent VATS operations. Second, in addition to existing endotracheal tubes, we could not exclude the hemodynamic effects from differences between positive pressure (IVAT) and negative pressure (NIVATS) ventilation. Although the Ce recorded from the target-controlled-infusion pump may not have caught up with the actual effect, the trends remained similar. Third, we did not test different concentrations of local anesthetics to determine the optimal regimen for TINBs. This may help to attenuate hemodynamic fluctuation, especially for older patients.

We concluded that the use of intraoperative multilevel TINBs with 0.5% bupivacaine adds deepening effects to anesthesia that are more than required for blunting responses to the subsequent uniport VATS. For IVATS, more analgesics, but not hypnotics, were required for IVATS than for NIVATS. With the trends of minimization of surgical stimulation, the anesthesiologists should bear the risk of oversubstitution or too deep anesthesia when they select the regional anesthesia and prepare the regimen.

**Abbreviations**

AP: artificial pneumothorax

ANOVA: analysis of variance
Declarations

Ethics approval and consent to participate:

This study was approved by the Research Ethics Committee of National Taiwan University Hospital, Taipei, Taiwan (201712125RINB) on February 2, 2018.

Consent for publication:

Not applicable.

Availability of data and materials:

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Figures
Figure 1

a. Mean arterial pressure (MAP), b. Ce of remifentanil, c. Heart rate (HR) d. Trends of BIS scores, e. Ce of propofol along with TINBs and VATS in both groups. Data are expressed as mean ± standard error. AP: artificial pneumothorax. TINBs: completion of TINBs from T3 to T8.
Figure 2

DSA changes after TINBs. Upper figure: TINBs in the IVATS group; lower figure: TINBs in the NIVATS group (arrow: TINBs after artificial pneumothorax). VATS started after TINBs completion.