ORIGINAL CLINICAL RESEARCH REPORT

OPEN

Phrenic Nerve Block at the Azygos Vein Level Versus Sham Block for Ipsilateral Shoulder Pain After Video-Assisted Thoracoscopic Surgery: A Randomized Controlled Trial

Kaori Kimura Kuroiwa, MD, PhD,* Yuki Shiko, MS,† Yohei Kawasaki, PhD,‡ Yoshitaka Aoki, MD,§ Masaaki Nishizawa, MD, PhD,* Susumu Ide, MD,* Kentaro Miura, MD, PhD,‖ Nobutaka Kobayashi, MD, PhD,‖ and Herman Sehmbi, MBBS, MD, EDAIC, EDRA¶

See Article, p 1592

BACKGROUND: Ipsilateral shoulder pain (ISP) is a common problem after pulmonary surgery. We hypothesized that phrenic nerve block (PNB) at the azygos vein level, near the location of the surgical operation, would be effective for reducing ISP. Our primary aim was to assess the effect of PNB on postoperative ISP, following video-assisted thoracic surgery (VATS).

METHODS: This prospective, randomized, patient-blinded, single-institution trial was registered at the University Hospital Medical Information Network (UMIN000030464). Enrolled patients had been scheduled for VATS under general anesthesia with epidural analgesia. Patients were randomly allocated to receive infiltration of the ipsilateral phrenic nerve at the azygos vein level with either 10 mL of 0.375% ropivacaine (PNB group) or 0.9% saline (control group) before chest closure. Postoperative ISP was assessed using a numerical rating scale (NRS, 0–10) at rest at 2, 4, 8, 16, and 24 hours. The incidence of ISP was defined as the proportion of patients who reported an NRS score of ≥1 at least once within 24 hours after surgery. In the primary analysis, the proportion of patients with ISP was compared between PNB and control groups using the χ^2 test. NRS values of ISP and postoperative incision pain within 24 hours were investigated, as was the frequency of postoperative analgesic use. Incision pain was assessed using an NRS at the time of ISP assessment. Finally, the incidence of postoperative nausea and vomiting and shoulder movement disorders were also evaluated.

RESULTS: Eighty-five patients were included, and their data were analyzed. These patients were randomly assigned to either PNB group (n = 42) or control group (n = 43). There were no clinically relevant differences in demographic and surgical profiles between the groups. There was no significant difference in the incidence of ISP (the control group 20/43 [46.5%] versus the PNB group 14/42 [33.3%]; $P = .215$). The severity of ISP was lower in the PNB group than in the control group (linear mixed-effects model, the main effect of treatment [groups]: $P < .001$). There were no significant differences between groups in terms of postoperative incision pain. The frequency of postoperative analgesic use was significantly higher in the control group (Wilcoxon rank sum test, $P < .001$). Postoperative nausea and vomiting did not significantly differ between the 2 groups. There were no changes in the range of shoulder joint movement.

CONCLUSIONS: Azygos vein level PNB did not significantly affect the incidence of ISP after VATS. (Anesth Analg 2021;132:1594–602)

KEY POINTS

- **Question:** Does phrenic nerve block (PNB) at the azygos vein level reduce ipsilateral shoulder pain (ISP) after video-assisted thoracic surgery (VATS)?

From the *Department of Anesthesia, Nagano Red Cross Hospital, Nagano, Japan; †Department of Biostatistics, Clinical Research Center, Chiba University Hospital, Chiba, Japan; ‡Department of Biostatistics of Japanese Red Cross College of Nursing, Tokyo, Japan; §Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, Hamamatsu, Japan; ‖Department of Thoracic Surgery, Nagano Red Cross Hospital, Nagano, Japan; and ¶Department of Anesthesia & Perioperative Medicine, London Health Sciences Centre, Western University, London, Ontario, Canada.

DOI: 10.1213/ANE.0000000000005305

Accepted for publication October 16, 2020.

Funding: None.

The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

Clinical trial number and registry URL: UMIN000030464 (http://www.umin.ac.jp/ctr/index/htm).

Reprints will not be available from the authors.

Address correspondence to Kaori Kimura Kuroiwa, MD, PhD, Department of Anesthesia, Nagano Red Cross Hospital, Wakasato 5-22-1, Nagano 380-8582, Japan. Address e-mail to anesthesi0hanz13@yahoo.co.jp.

- **Findings:** Although PNB at the level of the deformed vein did not reduce the incidence of ISP after VATS when considered as an anesthetic block, the post hoc analysis supports the role of this approach in the analgesic management of ISP.
- **Meaning:** PNB at azygous vein level is moderately effective in reducing ISP without absolving it completely.

GLOSSARY

BMI = body mass index; **CI** = confidence interval; **CONSORT** = Consolidated Standards of Reporting Trials; **FAS** = full analysis set; **FVC** = forced vital capacity; **HR** = heart rate; **ISP** = ipsilateral shoulder pain; **NRS** = numerical rating scale; **PCA** = patient-controlled epidural analgesia; **PNB** = phrenic nerve block; **PONV** = postoperative nausea or vomiting; **ROM** = range of motion; **SD** = standard deviation; **VAS** = visual analog scale; **VATS** = video-assisted thoracic surgery

Ipsilateral shoulder pain (ISP) commonly occurs after thoracic surgery.[1] The incidence of ISP is reportedly 31%–85%.[2] Notably, ISP is not effectively ameliorated by administration of local anesthetics through a thoracic epidural catheter, which is highly effective for incision pain.[3] ISP can impair respiration, mobility, and physical therapy in the early postoperative period[4]; it is also difficult to relieve pharmacologically.[1,5] Thus, an effective and safe solution for the management of ISP is needed.

ISP is considered to be the result of referred pain from irritation caused by surgical invasion to the pericardium, mediastinum, or diaphragm, transmitted via the phrenic nerve.[6,7] This mechanism is supported by the occurrence of ISP when phrenic nerve stimulation devices are used.[8] Furthermore, intraoperative phrenic nerve block (PNB) by local anesthetic infiltration of periphrenic fat tissue near the diaphragm has been reported to effectively reduce ISP.[6,9,10] However, at the level of the diaphragm, many sensory fibers from the pericardium and mediastinum have already left the phrenic nerve; therefore, targeting the phrenic nerve more cranially is presumably more effective.[6,11] To the best of our knowledge, no study has investigated the usefulness of local anesthetic infiltration around the phrenic nerve at the azygos vein level.

We hypothesized that infiltration of local anesthetic around the phrenic nerve at the azygos vein level would be effective for reducing ISP. The aim of this study was to test the effect of PNB on postoperative ISP following video-assisted thoracoscopic surgery (VATS), through assessment of the incidence of ISP after VATS.

METHODS

Study Design and Patient Enrollment

The study was approved by the bioethical committee of Nagano Red Cross Hospital (approval number: Nagano no. 131). This prospective, randomized, patient-blinded, single-institution trial was registered at the University Hospital Medical Information Network (identification number: UMIN000030464; principal investigator: Kaori Kimura Kuroiwa; date of registration: December 19, 2017) before patient enrollment. This trial was completed at Nagano Red Cross Hospital, Nagano, Japan, from December 2017 to December 2018. All procedures were performed in accordance with the Declaration of Helsinki, and the trial is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement. The principal investigator and coinvestigators screened patients for eligibility to participate in the study. The investigators explained the rationale of the study to patients who were eligible for study participation. Written informed consent was obtained from all enrolled patients. Inclusion criteria were as follows: patients scheduled for VATS, age >18 years, American Society of Anesthesiologists physical status level <III, and planned use of epidural anesthesia. Exclusion criteria were as follows: patients with contralateral paralysis of the phrenic nerve, allergy to ropivacaine, preoperative history of ISP, chronic pain, contraindications to epidural anesthesia, and/or dementia.

Block randomization for the intervention was implemented by the principal investigator (K.K.K.) using a computer-generated random number sequence. The computer-generated random number sequence was kept in the shared office for the 3 anesthesiologist's office to ensure that it was inaccessible to all but the 3 investigators. Patients were randomized in a 1:1 allocation ratio to either the intervention (PNB) group or the control group. Before arrival at the operating room, the anesthesiologist was told the patient's group allocation. We were unable to secure centralized drug dispensation and blinding through pharmacy and thus resorted to drug dispensing by the concerned anesthesiologist. While this unblinded the intraoperative team, none of these members were involved with data collection. The above 3 anesthesiologists took turns to collect the data, and it was devised so that the person in charge of anesthesia and the evaluator were different. It was difficult for 3 anesthesiologists to evaluate all points, so we asked a ward nurse to help with the evaluation. These nurses were blinded.

Anesthetic Technique and Analgesia

Before surgery, all patients completed routine pulmonary function tests. The day before surgery, they were evaluated for the range of shoulder joint motion by a physical therapist.

No patients had been premedicated. A peripheral intravenous line was placed in the forearm opposite to the surgical side. An arterial line was also placed into the radial artery for continuous invasive monitoring of arterial pressure. Intraoperative monitoring included continuous electrocardiography (leads II and V5), and heart rate (HR), invasive arterial pressure, arterial gas analysis (ABL 800; RADIOMETER, Tokyo, Japan), pulse oximetry, and end-tidal carbon dioxide concentration measurements. A midthoracic epidural catheter was inserted at the thoracic vertebra (T)5–T6 or T6–T7 interspace using the midline approach and the loss of resistance to saline technique. General anesthesia was induced with propofol (1.6 $mg \cdot kg^{-1}$) and remifentanil (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Muscle relaxation was achieved using rocuronium (0.6 $mg \cdot kg^{-1}$). After intubation, patients were placed in the lateral decubitus position. We ensured that the patient's upper arm was on an arm rest, fixed in a natural position, to avoid applying stress to and exceeding the range of motion (ROM) of the shoulder joint. Before the incision was made, a combination of fentanyl (100 μg) and 0.2% ropivacaine (8 mL) or a combination of morphine hydrochloride (2 mg) and 0.2% ropivacaine (10 mL) was administered in a bolus through an epidural catheter, regardless of the patient's body weight. The selection of morphine or fentanyl was determined by the attending anesthesiologist for each patient. Then, one or more 0.2% ropivacaine boluses (5 mL each) were administered if required to maintain systolic arterial pressure and HR within +20% of baseline values. General anesthesia was maintained using propofol and remifentanil. All procedures were performed by the same surgical team according to a standard surgical technique. At the end of the operation, a single chest tube was placed apically or with the tip positioned midposteriorly on a water seal.

While the surgeon was closing the chest, a patient-controlled epidural analgesia (PCA) infusion of ropivacaine 2 $mg \cdot mL^{-1}$ and fentanyl 4 $\mu g \cdot mL^{-1}$ or morphine hydrochloride 40 $\mu g \cdot mL^{-1}$ (baseline infusion: 3 $mL \cdot h^{-1}$ plus bolus doses of 3 mL; lockout period 30 minutes) was initiated. Propofol and remifentanil were discontinued at the end of surgery. After the last skin suture, the residual neuromuscular block was antagonized (sugammadex 2 $mg \cdot kg^{-1}$). Extubation was performed when the patients were judged to be awake and breathing regularly. The duration of the anesthetic procedure, surgical procedure, and lateral decubitus position were recorded. Postoperative analgesia consisted of a PCA infusion. The degree of pain was assessed using an 11-point numerical rating scale (NRS). Rescue analgesia was 3 mL of 0.2% ropivacaine through the epidural catheter. Patients were treated with intravenous acetaminophen 1 g when they requested an additional analgesic. The number of PCA flushes and number of acetaminophen doses used were recorded for each patient.

Phrenic Nerve Block

PNB was performed immediately before lung expansion and chest closure. Patients received infiltration of the ipsilateral phrenic nerve with either 10 mL of 0.375% ropivacaine (PNB group) or 0.9% saline (control group). The site of periphrenic infiltration is shown in Figure 1. The outer sleeve of a 19-gauge intravenous needle (Venula; Top Inc, Tokyo, Japan) was used as a 75-mm-length catheter. For right lung surgery, a small incision was made around the membrane of the phrenic nerve that runs at the level proximal to the junction of the azygos vein and superior vena cava, the tip of the catheter was inserted, and the drug was injected (Figure 2). For left lung surgery, a similar intervention was made to the phrenic nerve that runs above the level at which the accessory hemivenous vein joins the azygous vein. The incision was small to ensure that the drug would not overflow immediately after removal of the catheter. This procedure was performed by the operating surgeon.

Outcomes

We hypothesized that the PNB at this location will completely absolve ISP, that is, will be an anesthetic block. We defined the primary outcome, the incidence of ISP within 24 hours, as "the proportion of patients who reported an NRS score of ≥1 at least once within 24 hours after surgery." We assessed ISP at 2, 4, 8, 16, and 24 hours after surgery. The degree of shoulder pain was assessed at rest using an NRS, with 0 representing no pain and 10 representing the worst imaginable pain. We also conducted a post hoc analysis of our primary outcome, assuming the PNB to be analgesic block (NRS score of ≥4) to test the robustness of our hypothesis and results.

Secondary outcomes were NRS values of ISP and postoperative incision pain within 24 hours, as well as the frequency of postoperative analgesic use. Incision pain was also assessed using an NRS at 2, 4, 8, 16, and 24 hours after surgery. We also noted any postoperative nausea or vomiting (PONV) and measured it as a dichotomous outcome (yes/no). Finally, the range of shoulder movement was measured by the physical therapist at baseline and postoperatively, after the chest drain was removed.

Statistical Analysis and Sample Size

The primary outcome was the incidence of ISP (anesthetic definition). We compared the proportion

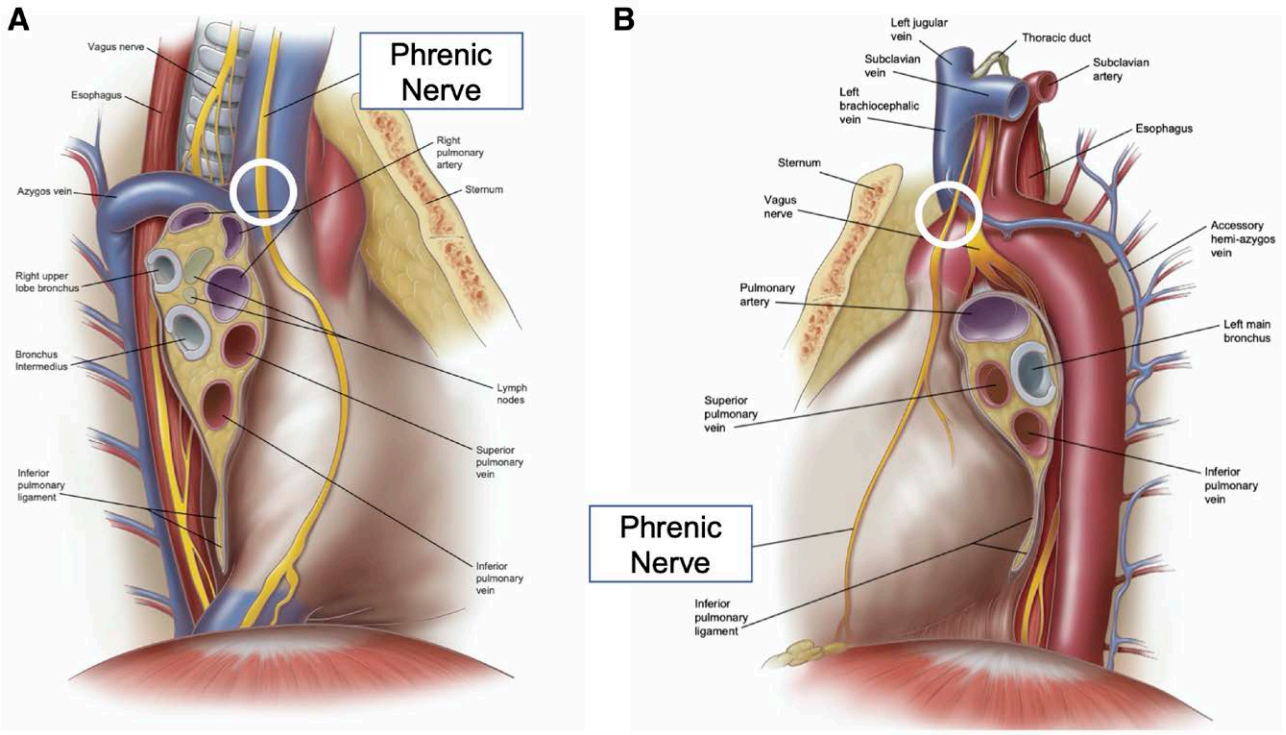

Figure 1. Diagram of periphrenic infiltration site. A, Right pulmonary hilum. B, Left pulmonary hilum. Region surrounded by white circle in figure indicates site of local anesthetic infiltration. Reprinted with permission from Warren and Milloy.[17]

of patients with ISP between the PNB and control groups using the χ^2 test. For the primary outcome, the numbers of patients allocated to the PNB and control groups who experienced ISP were recorded as the full analysis set (FAS). The post hoc analysis for ISP (using analgesic definition) was also conducted using the full set and χ^2 test. The significance level per comparison was set to $P = .025$ to account for multiplicity using Bonferroni method.[12]

In a secondary analysis, we used linear mixed-effects model to compare the ISP (assessed by NRS) between groups at each time point (2, 4, 8, 16, and 24 hours after surgery). We performed a logarithmic transformation of ISP scores (assessed by NRS), such that assumptions of a linear mixed model (including normal distribution of residuals) were upheld. For the mixed model, we designated the patients (ie, subjects) as a random effect (random intercept), while the time and group (including their interaction term) were treated as fixed effect.[12] We analyzed incisional pain (assessed by NRS) at each time point using a similar approach (linear mixed models). Additional details on linear mixed-effects model can be found in *Anesthesia & Analgesia*'s recent tutorial.[13] For pairwise between-group comparisons at the different time points, the significance criterion is set to 0.01 to account for multiplicity by the Bonferroni method.[14] We followed a similar method for analyzing the incisional pain scores.

The differences in analgesic consumption between the 2 groups were evaluated using the Wilcoxon rank sum test. The proportion of patients with PONV was compared between groups using the χ^2 test. The differences in the shoulder range of movement between the baseline and after surgery were compared using the Wilcoxon rank sum test. These tests were 2 tailed, and $P < .05$ was considered statistically significant for the secondary outcomes with no adjustment applied. All statistical analyses were performed using the SAS statistical software package, Version 9.4 (SAS Institute, Cary, NC).

Sample Size Estimation

The primary objective of present study was to compare the proportion of patients with ISP within 24 hours after surgery between the PNB and control groups. The null hypothesis was that there would be no significant between-group differences in the proportion of patients with ISP. Previous work has shown that the proportions of patients with ISP at 24 hours after surgery in a PNB group and a control group were 27% (10/37) and 60% (21/35), respectively.[10] Therefore, we calculated the sample size according to the expected proportions of patients with ISP in the PNB group (30%) and control group (60%). Based on these assumptions, the required sample size was 42 patients per group (2-sided, $\alpha = .05$, $\beta = .2$, χ^2 test). Considering a 15% dropout, we targeted at least 50 patients per group.

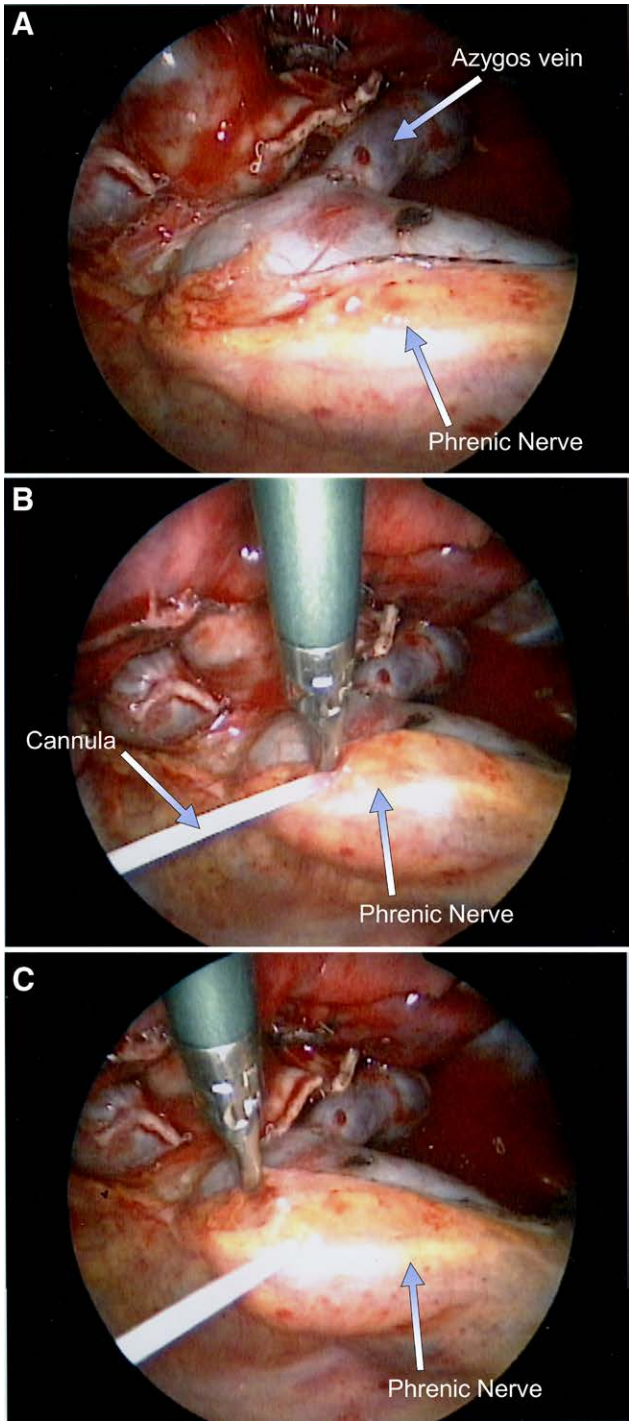

Figure 2. Phrenic nerve block: the method used in this study. A, Level proximal to junction of azygos vein and superior vena cava. B, Small incision was made in membrane around phrenic nerve running over superior vena cava. Cannula was inserted. C, Boluses of 0.375% ropivacaine (10 mL) for phrenic nerve block group and saline (10 mL) for control group were infiltrated around phrenic nerve. Swelling due to injection was observed.

RESULTS

In total, 100 patients were assessed for eligibility, and 85 were enrolled. The enrolled patients were randomly assigned to either the PNB group (n = 42) or the control group (n = 43) (Figure 3). One patient developed pneumonia and delirium, so NRS could only be evaluated 8 hours after surgery but was not excluded from the study. Planned VATS was converted to thoracotomy in 3 patients in the PNB group and 7 patients in control group. However, these patients were not excluded from the study. Patient demographic data and surgery characteristics, duration of the surgical procedure, lateral decubitus position, and anesthetic procedure were comparable between the 2 groups (Table 1).

The incidence of ISP within 24 hours was 20 of 43 (46.5%) in the control group versus 14 of 42 (33.3%) in the PNB group (difference = 13.2%; 95% confidence interval, −7.5 to 33.8; P = .215). The primary comparisons did not show a statistically significant difference. Post hoc analysis of primary outcome, assuming our block to be analgesic (NRS score of ≥4), rather than anesthetic (NRS score of ≥1), revealed that the incidence of ISP within 24 hours decreased significantly in the PNB group, compared with the control group (7/42 [16.7%] vs 20/43 [46.5%], diff =29.8; 95% confidence interval, 11.1-48.5; P = .003).

We analyzed the group differences in NRS scores using linear mixed models. The plots of the raw data of the NRS of ISP for each group and their mean values are shown in Figure 4A.

The severity of incisional pain was analyzed using linear mixed-effects model. The marginal means of group differences at each time points in post hoc tests revealed no significant differences between groups at any time point (Supplemental Digital Content, Table, http://links.lww.com/AA/D330). The plots of the raw data of the NRS of incisional pain for each group and their mean values are shown in Figure 4B.

The postoperative analgesic use was significantly less frequent in the PNB group (Wilcoxon rank sum test, P = .002). The incidences of PONV observed in the PNB and control groups were 16.7% and 16.3%, respectively (P = .960). There were no significant changes in the range of shoulder joint movement postoperatively (Table 2).

DISCUSSION

To the best of our knowledge, this is the first study to describe PNB at the azygos vein level for the treatment of postoperative ISP. The findings of this randomized controlled trial showed that infiltration of 10 mL 0.375% ropivacaine around the phrenic nerve at the azygos vein level did not affect the incidence of ISP after VATS, when ISP was defined as an "anesthetic block." However, when defining the PNB as an "analgesic block", the post hoc analysis of the same data revealed significant differences between the 2 groups. Moreover, analysis of NRS scores for ISP using linear mixed models showed that the PNB significantly reduced the severity of ISP and did not

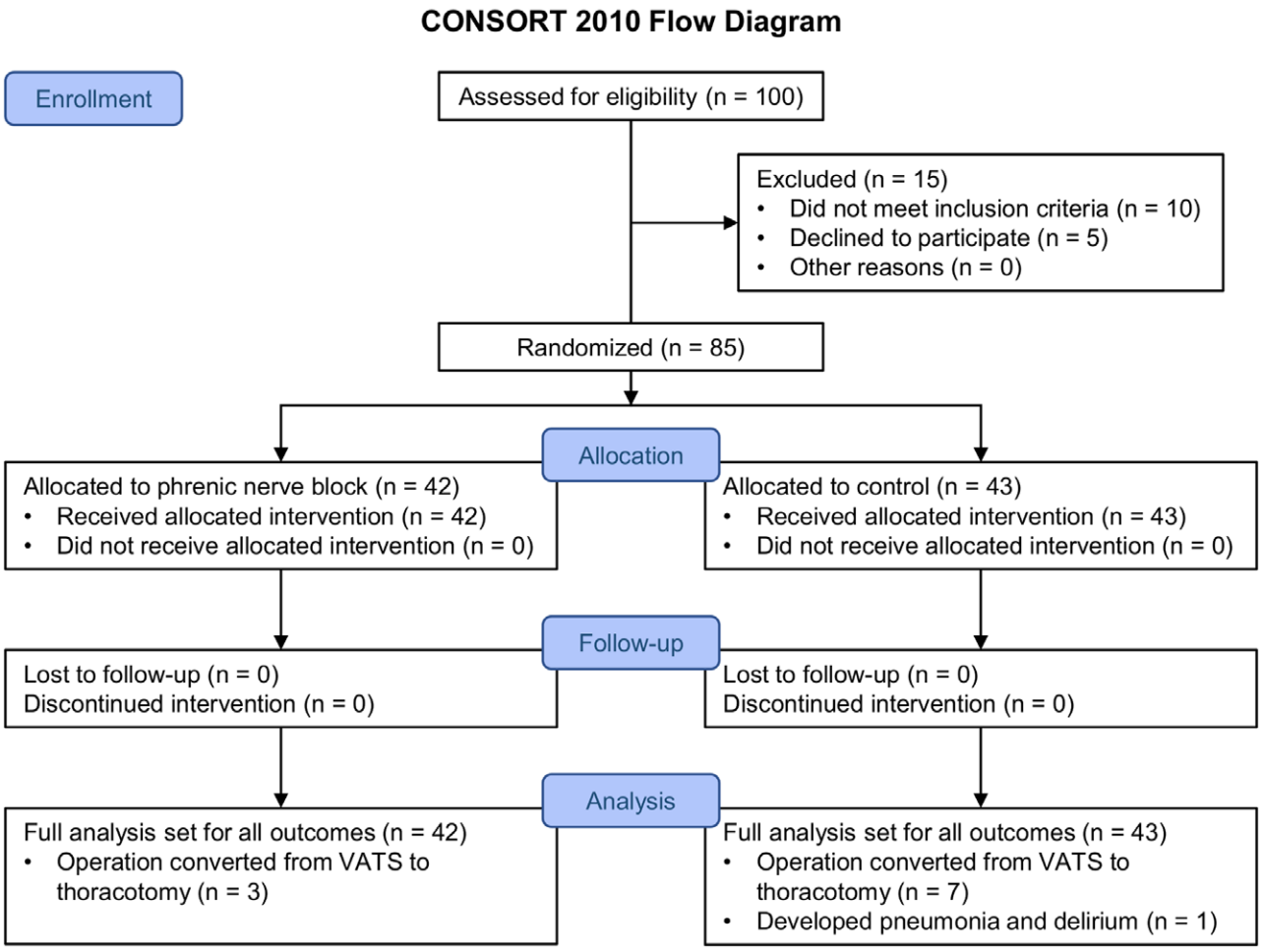

Figure 3. CONSORT flow chart for this study. CONSORT indicates Consolidated Standards of Reporting Trials; VATS, video-assisted thoracic surgery.

affect postoperative incision pain. No patients in this study experienced motor paralysis of the shoulder muscle as evidenced by unchanged ROM postoperatively. The proportion of patients with PONV did not differ between the 2 groups.

Our results are consistent with the findings of previous studies, in which PNB was effective for suppressing the severity of ISP. Reported methods for approaching the phrenic nerve include a cervical approach and a diaphragmatic approach. Suprascapular or interscalene brachial plexus blocks have been reported as the cervical approach to the phrenic nerve.[13,14] These procedures have been reported to produce motor block of the shoulder muscle and did not allow confirmation of the phrenic nerve by ultrasound in some patients.[14,15] In contrast, the diaphragm approach does not cause motor block of the upper extremity and allows confirmation of the phrenic nerve in all patients.[3,7,10] In our study, no patients had shoulder motor paralysis, and the phrenic nerve could be confirmed in all patients. However, the diaphragm approach does not allow sufficient access to the pericardium and mediastinum, which were the sites involved during lung resection. More proximal approaches to the phrenic nerve are currently under investigation.

While we were able to perform a proximal intrathoracic phrenic block under direct guidance in all of our cases, our approach could not completely alleviate ISP as evidenced by a marginal reduction in the incidence of ISP (33.3% vs 46.5%) with the PNB. This indirectly implies that perhaps PNB at this location is not an "anesthetic" block, but rather an "analgesic" block. It is likely that the cause of ISP may be related to irritation of the phrenic nerve, as well as multiple contributions from other factors (eg, stress on the shoulder joint or posterior thoracic ligaments). Thus, any one approach is unlikely to completely resolve this. It is interesting that when defined as an "analgesic" block, the PNB significantly reduced the incidence of ISP (16.7% vs 46.5%). This post hoc result supports the conjecture that PNB at azygos vein level is perhaps an "analgesic" block. This provides further support to the assertion that ISP after thoracic surgery is likely a "multi-factorial" phenomenon. However, this observation will need to be confirmed in future studies. Positioning patients for thoracic surgery is

essential; thus, the ability to suppressing severity of ISP by PNB would be of considerable benefit for patients. Nonsteroidal anti-inflammatory analgesics and acetaminophen are also effective for ISP. In our study, most patients in the PNB group used less acetaminophen after surgery. The combination of regular postoperative administration of acetaminophen with PNB may help patients to avoid ISP. It has been reported that local anesthetic administration to a thoracic epidural catheter results in no ISP inhibitory effect.[3] In the present study, we used opioids for epidural anesthesia. Some patients developed PONV in both groups due to opioid complications.

Our study has some limitations that warrant consideration. First, we did not evaluate diaphragmatic paralysis. Although markers of diaphragmatic paralysis (eg, ultrasound and X-ray) were available, they could not be accurately evaluated in the period immediately following surgery. Second, we did not perform pulmonary function tests after surgery.[16] In our study, there were no respiratory or any other major complications. However, in the control group, one patient experienced postoperative pneumonia. Third, the double-blind design could not be carried out as planned. The lack of a blinded assessor may have biased postoperative ISP assessment and could have led to differences in the careful of drug administration by surgeon. We overcame this limitation partly by ensuring that the assessors remained blind to the group allocation. Fourth, many patients with pneumothorax were included in the control group. However, these patients did not undergo pleurodesis, which is a presumed cause of ISP. Fifth, we only evaluated ISPs at rest. Most prior studies have considered ISP to be independent of movement.[1,2] Moreover, effective treatment of pain will reduce ISP severity, both at rest and during coughing.[9] Therefore, we presumed that a rest-only evaluation was sufficient. Finally, this study was underpowered to detect differences between groups in terms of rare events (eg, side effects or complications). Larger-scale studies are needed to clarify the risks of rarer complications, such as nerve injury. The PNB approach requires a portion of periphrenic

Table 1. Demographic and Surgical Profiles of the Patients

Variables	PNB group (n = 42)	Control group (n = 43)
Age (y), mean (SD)	66.4 (10.8)	62.5 (18.5)
Sex		
Male, n (%)	23 (54.8)	29 (67.4)
Female, n (%)	19 (45.2)	14 (32.6)
Etiology		
Pneumothorax, n (%)	1 (2.4)	4 (9.3)
Pulmonary cancer, n (%)	40 (95.2)	38 (88.4)
Others, n (%)	1 (2.4)	1 (2.3)
BMI (kg/m^2), mean (SD)	23.1 (2.6)	22.5 (3.4)
Duration of the surgical procedure (min), mean (SD)	213.2 (69.9)	182.4 (69.4)
Duration of the lateral decubitus position (min), mean (SD)	287.7 (68.0)	257.5 (105.7)
Duration of the anesthetic procedure (min), mean (SD)	238.4 (70.2)	208.4 (102.3)
Surgical approach		
Thoracotomy, n (%)	2 (4.8)	7 (16.3)
VATS, n (%)	40 (95.2)	36 (83.7)
Type of surgery		
Lobectomy, n (%)	38 (90.5)	30 (69.8)
Wedge resection, n (%)	3 (7.1)	12 (27.9)
Others, n (%)	1 (2.4)	1 (2.3)
Respiratory function		
Preoperative FVC %, mean (SD)	108.1 (24.0)	102.1 (15.6)
Preoperative FEV1.0%, mean (SD)	73.5 (9.5)	75 (9.6)

Abbreviations: BMI, body mass index; FVC, forced vital capacity; PNB, phrenic nerve block; SD, standard deviation; VATS, video-assisted thoracoscopic surgery.

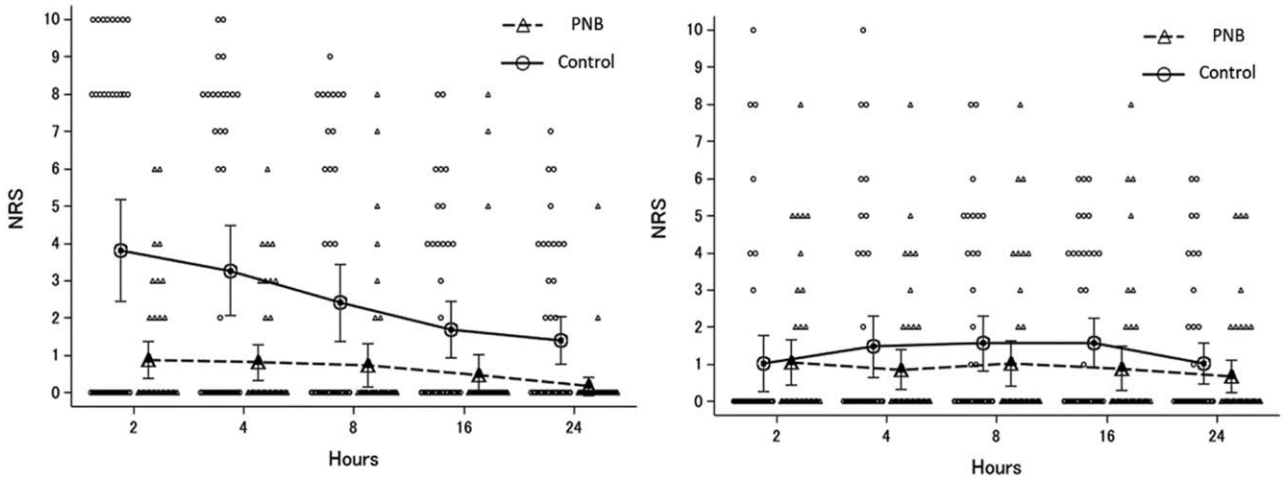

Figure 4. Severity of ISP (NRS) and postoperative incision pain (NRS). The figures depict raw NRS of patients underlay as a scatter plot, with averaged results superimposed on these (mean, 95% CI). A, Severity of ISP was significantly higher in control group than in PNB group after surgery. Log_{NRS} between 2 groups were significantly different at all time points in linear mixed models. B, No significant between-group differences were observed in severity of postoperative incision pain after surgery. Log_{NRS} between 2 groups were not significantly different at any time point in linear mixed models. Bars represent 95% CIs. CI indicates confidence interval; ISP, ipsilateral shoulder pain; NRS, Numeric Rating Scale; PNB, phrenic nerve block.

Table 2. Outcomes

	PNB group (n = 42)	Control group (n = 43)	*P*
The incidence of ISP[a,b]	14/42 (33.3%)	20/43 (46.5%)	.215
The incidence of ISP (post hoc)[a,c]	7/42 (16.7%)	20/43 (46.5%)	.003[d]
ISP NRS (mean, SD)[e]			
2 h	0.88 (1.67)	3.81 (4.50)	<.001[d]
4 h	0.81 (1.57)	3.26 (3.98)	<.001[d]
8 h	0.74 (1.90)	2.40 (3.41)	.006[d]
16 h	0.48 (1.77)	1.70 (2.54)	.009[d]
24 h	0.17 (0.82)	1.40 (2.12)	.007[d]
Incision pain NRS (mean, SD)[e]			
2 h	1.05 (2.00)	1.02 (2.52)	.664
4 h	0.86 (1.79)	1.48 (2.75)	.340
8 h	1.02 (2.05)	1.57 (2.46)	.195
16 h	0.88 (1.97)	1.58 (2.22)	.088
24 h	0.67 (1.44)	1.02 (1.87)	.452
Analgesic (median, IQR)[f] (no. of times acetaminophen was used)	0 (0–0)	1(0–2)	.002[d]
The incidence of PONV[a]	16.7%	16.3%	.960
Shoulder ROM (median, IQR)[f]			
Forward flexion: 1	170 (165–180)	170 (165–180)	.615
Backward extension: 1	50 (45–50)	50 (45–50)	.635
Abduction: 1	170 (160–180)	165 (155–180)	.445
Adduction: 1	0 (0–0)	0 (0–0)	
Forward flexion: 2	170 (160–180)	165 (160–180)	.971
Backward extension: 2	50 (45–50)	50 (40–50)	.102
Abduction: 2	170 (160–175)	160 (150–180)	.149
Adduction: 2	0 (0–0)	0 (0–0)	

Abbreviations: IQR, interquartile range; ISP, ipsilateral shoulder pain; NRS, numeric rating scale; PNB, phrenic nerve block; PONV, postoperative nausea and vomiting ; ROM, range of motion (in degrees); SD, standard deviation.

[a]χ^2 test.

[b]ISP as "Anesthetic" block: ISP defined as NRS >1 at any point within 24 h.

[c]ISP as "Analgesic" block: ISP defined as NRS >4 at any point within 24 h.

[d]Means a significant *P* value.

[e]Linear mixed models.

[f]Wilcoxon rank sum test.

membrane to serve as a reservoir; this membrane may be insubstantial in some patients. There is also a need to avoid intraneural injection. There is a risk of adding a block near the superior vena cava; damage to this vein can be fatal.

Despite these limitations, our study has several strengths. First, this is a first of its kind study testing a novel approach to PNB for relieving ISP. This block location is a familiar region for the thoracic surgeon improving the feasibility of the block. Second, in patients undergoing upper lobectomy, the phrenic nerve is easier to approach than the diaphragm, making our approach (proximal at the azygous vein level) easier than more distal diaphragmatic approaches.

In conclusion, infiltration of 0.375% ropivacaine around the phrenic nerve at the azygos vein level, performed by the surgeon before chest closure, is a simple analgesic technique that may suppress the severity of ISP after surgery. Future studies are needed to confirm our findings, besides investigating the anesthetic and analgesic potential of this novel approach.

ACKNOWLEDGMENTS

We thank Nia Cason, PhD, and Ryan Chastain-Gross, PhD, from Edanz Group (https://en-author-services.edanzgroup.com/) for editing a draft of this manuscript.

DISCLOSURES

Name: Kaori Kimura Kuroiwa, MD, PhD.
Contribution: This principle investigator was responsible for the conception and design of the study; data acquisition, analysis, and interpretation; and drafting of the manuscript. She has approved the manuscript to be published.
Name: Yuki Shiko, MS.
Contribution: This biostatistician performed all statistical analyses including sample size calculation and made a substantial contribution to the conception and design of the study, analysis and interpretation of the data, and drafting of the manuscript and its critical revision for important intellectual content. He has approved the manuscript to be published.
Name: Yohei Kawasaki, PhD.
Contribution: This biostatistician managed all statistical analyses including sample size calculation and made a substantial contribution to the conception and design of the study, analysis and interpretation of the data, and drafting of the manuscript and its critical revision for important intellectual content. He has approved the manuscript to be published.
Name: Yoshitaka Aoki, MD.
Contribution: This author made a substantial contribution to the conception and design of the study, analysis and interpretation of the data, and drafting of the manuscript and its critical revision for important intellectual content. He has approved the manuscript to be published.
Name: Masaaki Nishizawa, MD, PhD.
Contribution: This author made significant contributions to the research design and data collection, and wrote and revised important intellectual content. He agrees to be responsible for all aspects of the study, with a final review and approval before submission.

Name: Susumu Ide, MD.
Contribution: This author made significant contributions to research design and data collection, and wrote and revised important intellectual content. He has agreed to be responsible for all aspects of the study, with a final review and approval before submission.
Name: Kentaro Miura, MD, PhD.
Contribution: This author made a significant contribution to data collection. In addition, he wrote and revised intellectual content and has approved submission of the paper. He has also agreed to be responsible for all aspects of this research.
Name: Nobutaka Kobayashi, MD, PhD.
Contribution: This author made a significant contribution to data collection. In addition, he wrote and revised intellectual contents, and approved the manuscript before submission. He has also agreed to be responsible for all aspects of this research.
Name: Herman Sehmbi, MBBS, MD, EDAIC, EDRA.
Contribution: This author made a substantial contribution to the analysis and interpretation of the data, and drafting the final version of the manuscript. He has approved the manuscript to be published.
This manuscript was handled by: Richard Brull, MD, FRCPC.

REFERENCES

1. Burgess FW, Anderson DM, Colonna D, Sborov MJ, Cavanaugh DG. Ipsilateral shoulder pain following thoracic surgery. *Anesthesiology*. 1993;78:365–368.
2. Yousefshahi F, Predescu O, Colizza M, Asenjo JF. Postthoracotomy ipsilateral shoulder pain: a literature review on characteristics and treatment. *Pain Res Manag*. 2016;2016:3652726.
3. Barak M, Ziser A, Katz Y. Thoracic epidural local anesthetics are ineffective in alleviating post-thoracotomy ipsilateral shoulder pain. *J Cardiothorac Vasc Anesth*. 2004;18:458–460.
4. Li WW, Lee TW, Yim AP. Shoulder function after thoracic surgery. *Thorac Surg Clin*. 2004;14:331–343.
5. Mac TB, Girard F, Chouinard P, et al. Acetaminophen decreases early post-thoracotomy ipsilateral shoulder pain in patients with thoracic epidural analgesia: a double-blind placebo-controlled study. *J Cardiothorac Vasc Anesth*. 2005;19:475–478.
6. Scawn ND, Pennefather SH, Soorae A, Wang JY, Russell GN. Ipsilateral shoulder pain after thoracotomy with epidural analgesia: the influence of phrenic nerve infiltration with lidocaine. *Anesth Analg*. 2001;93:260–264.
7. MacDougall P. Postthoracotomy shoulder pain: diagnosis and management. *Curr Opin Anaesthesiol*. 2008;21:12–15.
8. Morélot-Panzini C, Le Pimpec-Barthes F, Menegaux F, Gonzalez-Bermejo J, Similowski T. Referred shoulder pain (C4 dermatome) can adversely impact diaphragm pacing with intramuscular electrodes. *Eur Respir J*. 2015;45:1751–1754.
9. Danelli G, Berti M, Casati A, et al. Ipsilateral shoulder pain after thoracotomy surgery: a prospective, randomized, double-blind, placebo-controlled evaluation of the efficacy of infiltrating the phrenic nerve with 0.2%wt/vol ropivacaine. *Eur J Anaesthesiol*. 2007;24:596–601.
10. Martinez-Barenys C, Busquets J, de Castro PE, et al. Randomized double-blind comparison of phrenic nerve infiltration and suprascapular nerve block for ipsilateral shoulder pain after thoracic surgery. *Eur J Cardiothorac Surg*. 2011;40:106–112.
11. Blichfeldt-Eckhardt MR, Laursen CB, Berg H, et al. A randomised, controlled, double-blind trial of ultrasound-guided phrenic nerve block to prevent shoulder pain after thoracic surgery. *Anaesthesia*. 2016;71:1441–1448.
12. Li G, Taljaard M, Van den Heuvel ER, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. *Int J Epidemiol*. 2017;46:746–755.
13. Schober P, Vetter TR. Repeated measures designs and analysis of longitudinal data: if at first you do not succeed-try, try again. *Anesth Analg*. 2018;127:569–575.
14. Šidák Z. Rectangular confidence regions for the means of multivariate normal distributions. *JASA*. 2012;10:626–633.
15. Bunchungmongkol N, Pipanmekaporn T, Paiboonworachat S, Saeteng S, Tantraworasin A. Incidence and risk factors associated with ipsilateral shoulder pain after thoracic surgery. *J Cardiothorac Vasc Anesth*. 2014;28:979–982.
16. Saha S, Brish EL, Lowry AM, Boddu K. In select patients, ipsilateral post-thoracotomy shoulder pain relieved by suprascapular nerve block. *Am J Ther*. 2011;18:309–312.
17. Warren WH, Milloy FJ. Pulmonary vascular system and pulmonary hilum. *Thorac Surg Clin*. 2007;17:601–617.