〈Regular Article〉

Effects of serratus plane block and epidural analgesia on stress hormones after thoracoscopic lung surgery: a randomized trial.

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ABSTRACT Serratus-intercostal plane block (SPB) is performed in thoracic surgery and breast cancer surgery because it is safer and easier to perform than epidural anesthesia. However, the effect of SPB on stress hormones has not been investigated.

Patients with lung cancer who were scheduled to undergo video-assisted thoracoscopic surgery (VATS) during the period from September 2017 to April 2018 were included in this single-center randomized trial. The institutional ethics committee approved this study (approval No. 2802-1). Patients were assigned to group B (SPB) or group E (epidural anesthesia). Levobupivacaine was administered as a local anesthetic to either the epidural space or serratus plane space. Blood samples were taken to measure levels of stress hormones including adrenaline, noradrenaline, dopamine, cortisol, and glucose at the induction of anesthesia and on the day following surgery.

Sixteen patients were included in the current study. Seven of those patients were assigned to group B and the other 9 patients were assigned to group E. Plasma adrenaline level in group B was significantly higher than that in group E postoperatively (P = 0.007). However, other markers were not different between the two groups, and there was no difference in pain scores between the two groups. In conclusion, SPB is an alternative analgesic method to epidural anesthesia in patients undergoing VATS. doi：10.11482/KMJ-E201945053 *(Accepted on June 17, 2019)*
Key words：Serratus plane block, Epidural analgesia, Stress hormones, Video-assisted thoracoscopic surgery

INTRODUCTION

Epidural analgesia has been used for intraoperative and postoperative pain management in thoracotomy because classical thoracotomy causes severe postoperative pain[1)]. Video-assisted thoracic surgery (VATS) for lung resection is now widely performed in order to reduce surgical stress. However, epidural anesthesia is used less frequently used than now because the surgical scar is smaller when VATS is used and because more patients who undergo

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surgery are taking anti-platelet or anti-coagulation drugs. Instead of epidural anesthesia, a peripheral nerve block for postoperative pain management has become popular with developments in ultrasound technology. Serratus-intercostal plane block (SPB) is now widely performed in thoracic surgery and breast cancer surgery because it is safer and easier to perform than epidural anesthesia[2].

Surgical stress causes tissue damage followed by production of inflammatory cytokines that promote secretion of stress hormones in the hypothalamus. These hormones and also pain cause sympathetic stimulation that leads to increases in heart rate, blood pressure, and serum glucose[3]. It has been reported that secretion of stress hormones causes hyperglycemia, which can lead to surgical site infection and renal failure[4, 5]. Epidural analgesia inhibits the secretion of cortisol and adrenaline by blocking the sympathetic nervous system[6]. The effect of a paravertebral block during VATS on stress hormones has been reported[7], but there has been no report on the effect of SPB on levels of stress hormones. In the present study, we investigated the effects of SPB and epidural anesthesia on levels of stress hormones in patients undergoing VATS under general anesthesia.

METHODS

Participants

Patients with lung cancer who were scheduled to undergo video-assisted thoracoscopic surgery (VATS) during the period from September 2017 to April 2018 were included in this trial. This study was approved by the institutional ethics committee of Kawasaki Medical School (approval No. 2802-1) and written informed consent was obtained from the patients or their guardians. This trial was registered at University Hospital Medical Information Network Clinical Trials Registration (UMIN CTR) (https://www.umin.ac.jp/ctr/index.htm) (regstration No. 28338).

Group allocation and randomization sequence

Randomization was stratified by closed envelopes in which either "epidural" or "block" was written on papers. One of the papers was drawn from the envelope for each patient. The same papers and envelopes were iteratively used in the whole study period. According to the papers, each patient was allocated to either group B (block) or group E (epidural). The primary endpoint of this study was changes in levels of stress hormones. We investigated the changes in levels of stress hormone in patients undergoing VATS under general anesthesia with epidural analgesia or SPB analgesia. We also assessed NRS, postoperative administration of non-opioid analgesics, and amount of fentanyl for IV PCA as secondary endpoints.

Surgical procedures and anesthesia

Intravenous access was obtained in the operating theater and then the patient was turned to a lateral decubitus position. An epidural catheter was placed at the Th7/8 level in all patients. After the patient had been placed in the supine position, general anesthesia was induced with 1 mg/kg of propofol, fentanyl at a dose of 50 μg to 200 μg, and remifentnil at a dose of 0.25 μg/kg/min. The trachea was intubated with a dual-lumen endotracheal tube following rocuronium administration. A radial arterial line was inserted after the position of the endotracheal tube had been confirmed by bronchoscopic examination. Anesthesia was maintained with propofol infusion (target control) or an inhalational agent such as sevoflurane or desflurane.

Thoraco port® (11.5 mm) was placed at the 7th intercostal space (ventral side) for thoracoscopy after the patient had been placed in the lateral decubitus position. A small skin incision was made at the 4th intercostal space for upper lobe lobectomy or at the 5th intercostal space for lower lobe lobectomy. Lobe resection was carried out with

the aid of another two insertion ports for surgical assistance (7th or 8th intercostal space, dorsal side).

Analgesia

Patients allocated to group E received epidural anesthesia with 5 mL of 0.25% levobupivacaine through an epidural catheter before the skin incision for surgery was made followed by continuous infusion of 0.25% levobupibvacaine at the rate of 4 mL/hr. Intravenous patient-controlled analgesia (IV-PCA) with fentanyl was initiated at the end of surgery. A 100-ml solution was made by diluting 1,000 μg of fentanyl and 5 mg of droperidol with 98 mL of normal saline. IV-PCA was set at base infusion of 2 mL/hr, bolus of 2 mL, lockout of 15 min, and maximum allowed frequency of 4 times/hr.

All of the patients allocated to group B received SPB. An ultrasound probe was placed vertically against the skin incision line and a 22 G needle was longitudinally inserted under ultrasound guidance. The tip of the needle was placed between the anterior serratus muscle and intercostal muscle, and 20 mL of 0.25% levobupivacaine was administered as described elsewhere[8]. Spread of the local anesthetic was confirmed by ultrasound images. Normal saline was administered at the rate of 4 mL/hr through an epidural catheter in patients allocated to group B. IV-PCA was initiated at the same dose as that for patients in group E. Intravenous acetaminophen or flurbiprofen axetil was given when patients requested additional pain treatment on the day of surgery. IV-PCA was basically ceased on postoperative day 1, and celecoxib and acetaminophen were regularly administered as oral analgesic medication.

Measurements of the levels of stress hormones

Blood samples were taken through an intraarterial line before tracheal intubation and after surgery. The specimens were transferred to a laboratory company (SRL®) and plasma levels of adrenaline, noradrenaline, dopamine, and cortisol were measured. Plasma levels of adrenaline, noradrenaline, and dopamine were measured using high-performance liquid chromatography, cortisol was measured by ECLIA, and glucose was measured by the hexokinase UV method.

Assessment of pain

A physician or nurse asked patients to assess their level of pain using a numerical rating scale from 0 to 10 (NRS) at 1 hr, 6 hr, 12 hr, 24 hr, and 48 hr after surgery. Requirement of extra analgesics, postoperative nausea and vomiting, hypotension, respiratory depression and delirium were recorded as adverse events.

Statistical analysis

Based on a previous report, it was estimated that the mean plasma level of postoperative adrenaline in group E would be 150 pg/mL and that the mean plasma level of adrenaline in group B would be double that in group E[9]. Standard deviation was set at 100. Alfa error was determined to be 0.05 and beta error was determined to be 0.2. Thus, the required number was 7 in each group. Continuous numbers are presented as means (95% confidence interval) or medians (interqurtile range) as appropriate. Comparisons were made by Student's t-test for continuous variables and by Fisher's exact test for categorical data. Statistical significance was determined at a p value less than 0.05. Analysis was performed using JMP® 10 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patients' demographics

There were 41 patients as candidates during the study period. Sixteen patients were included in the current study. Seven of those patients were allocated to group B and the other 9 patients were allocated to group E. All of the participants completed the study

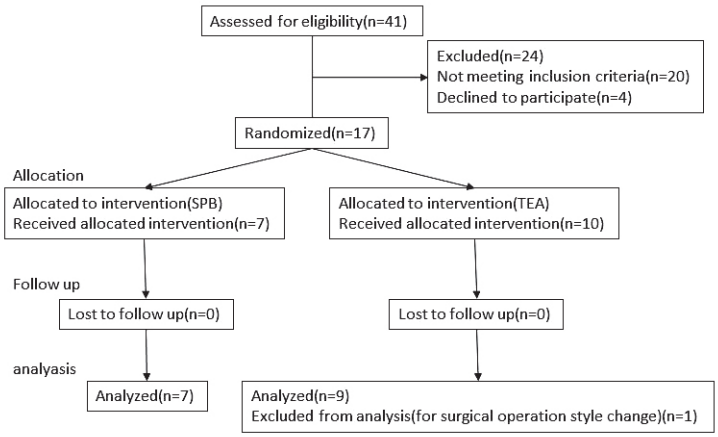

Fig. 1. Patients' flow diagram.

Table 1. Baseline characteristics of the patients

	Group B (n=7)	Group E (n=9)	P value
Sex (male)	3 (42.9%)	5 (55.6%)	0.500
Age (year)	69.3 (61.3-77.3)	63.8 (56.7-70.8)	0.285
Height (cm)	156.8 (150.4-163.2)	162.5 (156.9-168.1)	0.183
Body weight (kg)	57.1 (50.0-64.2)	54.8 (48.5-61.0)	0.634
Duration of surgery (min)	176.3 (137.3-215.3)	217.8 (183.4-252.2)	0.086
Duration of anesthesia(min)	238.9 (199.0-278.7)	259.1 (224.0-294.3)	0.428
Duration of one-lung ventilation (min)	173.7 (116.4-231.0)	237.4 (186.9-288.0)	0.074

Data are presented as mean (95% CI) or number of patients (%). Group B: serratus-intercostal plane block (SPB); Group E: thoracic epidural analgesia

protocol (Fig. 1). Age, gender, height, and body weight were not significantly different between the two groups. There were also no significant differences in the duration of surgery and the duration of one-lung ventilation between the two groups (Table 1).

Stress hormones

Plasma concentrations of noradrenaline, dopamine, cortisol and glucose were not significantly different between the two groups in both preoperative and postoperative measurements (Table 2). However, plasma adrenaline level in group B was significantly higher than that in group E postoperatively (P = 0.007). There was also a significant increase from preoperative to postoperative plasma levels for adrenaline but not for other hormones.

Analgesic effects

There was no significant difference in NRS between the two groups at any time point (1 hour, 6 hours, 12 hours, 24 hours, and 48 hours after surgery) (Table 3). The amounts of supplementary analgesics up to 24 hours were not different in the two groups. The amounts of fentanyl consumption in IV-PCA in subsequent periods were also not significantly different between the two groups because all of the patients regularly took oral analgesics (Table 4).

The incidences of nausea, vomiting, hypotension, respiratory depression, and delirium were not significantly different between the two groups. Major complications of regional anesthesia such as infection and bleeding did not occur in any of the patients in this study.

Table 2. Changes in levels of stress hormones

	Group B (n=7)	Group E (n=9)	P
Adrenaline (pg/ml)			
Pre ope	48.4 (19.0-77.9)	25.7 (-0.2-51.8)	0.236
Post ope	393.5 (282-504.0)	179.2 (81.7-276.8)	0.007
Δchange	345.0 (236.0-453.6)	153.4 (57.7-249.2)	0.013
Noradrenaline (pg/ml)			
Pre ope	507.5 (232.2-782.2)	493.4 (251.0-735.9)	0.937
Post ope	624.2 (446.0-802.3)	514.9 (357.7-672.0)	0.341
Δchange	116.9 (-59.2-292.5)	21.4 (-133.9-176.7)	0.398
Dopamine (pg/ml)			
Pre ope	23.6 (12.6-34.5)	16.0 (6.3-25.7)	0.285
Post ope	28.1 (20.6-35.7)	21.4 (14.8-28.1)	0.176
Δchange	4.6 (-3.6-12.8)	5.4 (-1.8-12.7)	0.866
Cortisol (μg/dl)			
Pre ope	12.4 (9.5-15.3)	12.9 (10.3-15.4)	0.806
Post ope	22.8 (14.6-31.0)	25.2 (18.0-32.5)	0.635
Δchange	10.4 (2.7-18.0)	12.4 (5.7-19.1)	0.677
Glucose (mg/dl)			
Pre ope	107.7 (97.7-117.8)	101.9 (93.0-110.7)	0.366
Post ope	145.0 (120.7-169.3)	135.1 (113.7-156.5)	0.528
Δchange	37.3 (15.6-59.0)	33.2 (14.1-52.3)	0.767

Data are presented as mean (95% CI). Group B: serratus-intercostal plane block (SPB), Group E: thoracic epidural analgesia.

Table 3. Postoperative NRS scores and additional analgesic requirement

	Group B (n=7)	Group E (n=9)	P
After 1h	3.7 (1.4-6.1)	3.11 (1.1-5.2)	0.684
After 6h	3.0 (1.5-4.5)	1.56 (0.2-2.9)	0.145
After 12h	2.0 (0.4-3.6)	1.67 (0.2-3.1)	0.710
After 24h	1.0 (-0.1-2.1)	1.0 (-0.0-2.0)	1.000
After 48h	0.57 (-0.2-1.4)	1.0 (0.3-1.7)	0.405
Additional analgesic (number of doses per case)			
within 12h	1 (0-3)	0 (0-1)	0.0886
Within 24h	1 (0-5)	0 (0-1)	0.0524

Data are presented as mean (95% CI) or number of patients (%). Group B: serratus-intercostal plane block (SPB); Group E: thoracic epidural analgesia

Table 4. Postoperative total consumption of IV-PCA

	Group B（n=7）	Group E（n=9）	P
After 1h (ml)	5.7 (4.16-7.26)	5.3 (3.96-6.70)	0.6992
After 6h (ml)	19.4 (16.67-22.18)	16.2 (13.79-18.64)	0.0819
After 12h (ml)	30.6 (26.2-34.88)	29.6 (25.75-33.35)	0.7103
After 24h (ml)	49.3 (34.73-63.8)	59.2 (46.375-72.03)	0.2900

Data are presented as median (interquartile range). IV-PCA: intravenous patient- controlled analgesia, Group B: serratus-intercostal plane block (SPB), Group E: thoracic epidural analgesia.

DISCUSSION

In this trial, plasma adrenaline level was significantly higher in patients receiving serratus plane block than in those with epidural anesthesia for lung resection surgery. It is well known that epidural analgesia inhibits the actions of not only sensory nerves but also the sympathetic nervous system against surgical stress followed by deceleration of hypothalamus activation[10]. Many previous studies showed that general anesthesia with epidural analgesia successfully inhibited the activation of stress hormone systems compared

with general anesthesia alone. Kawagoe *et al.* found that dopamine, cortisol, and glucose levels were significantly lower in the epidural group in their study[11]. There were no significant differences in dopamine, cortisol, and glucose in our study because it is thought signal transduction in the stress hormone system was suppressed to some degree by SPB. In another study, it was found that plasma adrenaline and noradrenaline levels in patients undergoing esophageal surgery were significantly lower in the epidural group than in the general anesthesia alone group[12]. Since adrenaline level was significantly higher in group B in our study, the effect of SPB on sympathetic nerves might not be as strong as the effect of epidural analgesia.

Thus, the results of many studies have suggested that epidural anesthesia inhibits the secretion of stress hormones. However, the effect of SPB on stress hormone secretion has not been clarified.

Richardson *et al.* compared levels of stress hormones and postoperative pain in patients with a paravertebral block and those with epidural analgesia. In their study, cortisol and glucose levels were significantly lower in the paravertebral group[5].

However, the dose of bupivacaine administered in the paravertebral group was two-times larger than that administered in the epidural group in that study. This is supported by the results of another study showing that a higher dose of lidocaine for epidural analgesia inhibited the increase in adrenaline[13].

Since the plasma level of adrenaline was higher in group B than in group E in our study, one possible mechanism for the increase in adrenaline level is the weaker effect of SPB on the spinal dorsal horn. The total dose of bupivacaine in group E might have been larger than that in group B since continuous infusion was given in group E, although the initial bolus dose of bupivacaine in group B was four-times larger than that in group E. This may be a key issue for understanding the results of our study.

In this study, there were no differences between the two groups in the amount of fentanyl used, levels of stress hormones other than adrenaline, glucose level and pain score. Given the fact stated above, SPB has inhibitory effects equivalent to those of epidural anesthesia on intraoperative and postoperative pain and on unfavorable reactions. In a previous study, the effect of SPB during VATS was investigated and it was shown that the use of postoperative supplemental analgesics was significantly less in patients who received SPB, and a similar study showed that pain scores according to NRS were lower and postoperative analgesic consumption was less in the SPB group than in the control group[14, 15]. Those results are consistent with our results.

There are some limitations in this study. Although this study was a prospective randomized trial, NRS score was based on assessment by patients and generalizability is thus unclear. Blinding of analgesia methods was difficult, also limiting generalizability.

CONCLUSIONS

Although plasma adrenaline level in patients receiving a serratus plane block is higher than that in patients receiving epidural anesthesia, post-operative blood glucose levels or NRS are similar compared with epidural anesthesia and this block is an alternative analgesic method to epidural anesthesia in patients undergoing VATS.

CONFLICT OF INTEREST

All authors have no conflict of interests.

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