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The benefits of preincision ropivacaine infiltration for reducing postoperative pain after robotic bilateral axillo-breast approach thyroidectomy: a prospective, randomized, double-blind, placebo-controlled study

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Purpose: The aim of this study was to evaluate the effects of preoperative ropivacaine infiltration in patients undergoing robotic thyroidectomy using the bilateral axillary breast approach method.
Methods: Using a randomized, double-blind study design, 34 consecutive female patients who underwent robotic thyroidectomy were randomly assigned to receive local infiltration to the skin flap site using either only 0.9% saline solution, 3 mL/kg (group C, n = 17) or 0.1% ropivacaine with saline, 3 mg/kg (group L, n = 17). Local anesthetic was administered prior to skin incision after the induction of general anesthesia. Postoperative pain was rated at 2, 6, 18, 30, 42, and 66 hours postoperatively by visual analogue scale (VAS) score. The bottom hit counts (BHC) from patient controlled analgesia and fentanyl consumption were evaluated. CRP levels, mean blood pressure (BP), and heart rate (HR) were also evaluated.
Results: VAS pain scores were significantly lower in group L than in group C from 2 to 42 hours ($P < 0.05$). Fentanyl use for analgesia and BHC were also significantly lower in group L compared with group C during the first postoperative 6 and 2 hours, respectively ($P < 0.05$). The total consumption of fentanyl was significantly lower in group L than in group C ($P = 0.009$). No significant differences were noted for baseline, postoperative mean BP, or HR.
Conclusion: Preoperative infiltration using ropivacaine with saline to all flap sites is a safe and effective method for reducing postoperative pain and postoperative fentanyl consumption in patients with robotic thyroidectomy.
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Key Words: Robotics, Thyroidectomy, Pain

INTRODUCTION

Differentiated thyroid carcinoma has been the most common carcinoma among female patients in South Korea since 2004, and the incidence has increased every year [1]. Most young female patients with asymptomatic thyroid carcinoma are concerned with surgical scarring as well as oncologic completeness. Patients of African and East Asian descent tend to develop more prominent scars than those of European descent [2]. The remote approach from the neck using endoscopic or robotic instruments was developed to avoid neck scarring and these approaches have acceptable oncologic safety [3-8].

Endoscopic and robotic thyroidectomy require wide flap dissection to ensure sufficient working space, because the

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neck does not have natural free space. Ryu et al. [9] reported that the width of the flap required for transaxillary robotic thyroidectomy was more than three times that used in conventional open thyroidectomy. We have performed robotic thyroidectomy using the bilateral axillary breast approach (BABA), which also requires greater extents of flap dissection bilaterally. The intensity of pain in patients undergoing robotic thyroidectomy differs according to study. Tae et al. [10,11] reported that patients undergoing robotic thyroidectomy showed higher pain scores than those undergoing open thyroidectomy in the immediate postoperative period, but Ryu et al. [9] reported no differences in pain score between the two groups. Although many studies related to robotic thyroidectomy have shown good cosmetics and feasibility, efforts to reduce pain related to surgery are still lacking.

Efforts to reduce postoperative pain, referred to as preventive analgesia, are common in other types of surgeries. Preoperative local infiltration with anesthetics to the operation site is easy and has shown good effects in abdominal, thoracic, and plastic surgical contexts. The aim of the present study was to evaluate the effects of preoperative ropivacaine infiltration in patients undergoing robotic thyroidectomy using the BABA method.

METHODS

Patients

The study protocol was approved by the Institutional Review Board of the Chung-Ang University College of Medicine and registered with the Clinical Research Information Service (KCT0000555, *http://cris.nih.go.kr*). This study was carried out according to the principles of the Declaration of Helsinki (2000), and written informed consent was obtained from all participants before inclusion.

A total of 34 consecutive female patients who underwent robotic thyroidectomy between December 2012 and July 2013 were eligible for enrollment in the study. Male patients or patients with side effects of local anesthetics were excluded. The decision to enroll or exclude each patient was made by an investigator who did not otherwise participate in conducting the study or collecting data.

Study design and randomization

This was a randomized, double-blinded, placebo-controlled study. Randomization into one of two groups was based on a random table generated using PASS 11 (NCSS, Kaysville, UT, USA). The randomization sequence was generated by a statistician who was not otherwise involved with the study. The details of the series were unknown to the investigators who participated in conducting the study, and the group assignments were kept in sealed envelopes, each bearing only the case number on the outside. After recruitment, each patient was given a case number, and after admitting the patient into the operating room and just before the induction of anesthesia, the numbered envelope was opened and the card inside used to determine into which group the patient would be placed. The infiltration fluids were prepared by an additional investigator who read the group assignment cards without communicating patient status to the surgeon and anesthesiologist. In order to keep the surgeon and the anesthesiologist "blind" to the patient's status, patients received either normal saline with ropivacaine or only normal saline as placebo without distinguishing treatments by label. The patients assigned to group L received 3 mL/kg of 0.1% saline mixed ropivacaine (dose: 3 mg/kg), while group C received the same amount of 0.9% saline solution for preincisional infiltration of the skin flap site. The maximum dose of ropivacaine was limited to 200 mg.

All parties involved, including the patients, the surgeon, the anesthesiologists, and the investigator collecting the data, were unaware of the study drugs or the patient's group assignment.

General anesthesia

All patients received the same anesthetic protocol. The patients did not receive premedication, and anesthesia was induced with intravenous 2 mg/kg of propofol and 0.8 mg/kg of rocuronium. Anesthesia was maintained using 2%–3% sevoflurane in 1-L/min nitrous oxide (N_2O), and 1-L/min O_2. No additional intravenous opioids were injected during surgery.

Surgical techniques

The fluid prepared for study treatments was infiltrated into the subcutaneous tissue of the skin flap site using 23-gauge needle before skin incision. The infiltration lesion was bounded superiorly by thyroid cartilage, inferiorly by a line 2 cm below the clavicle, and laterally by the lateral border of the sternocleidomastoid muscle including trocar site (Fig. 1).

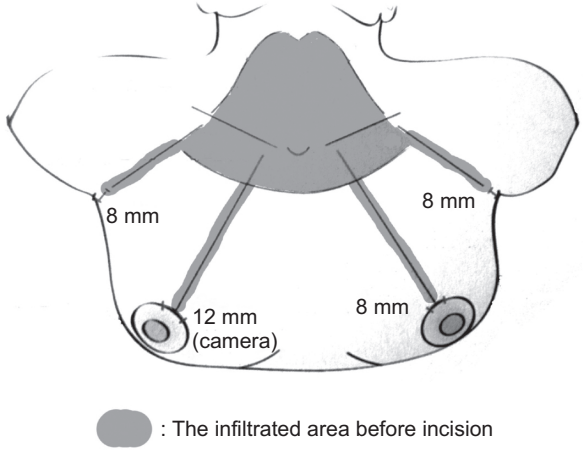

Fig. 1. The wide robot flap dissection area. The infiltrated area before incision.

After the preincisional infiltration was completed, a 12-mm circumareolar incision was made in the right breast for the camera port. For the remainder of the trocar access points, an 8-mm left circumareolar incision was made, as well as 8-mm incisions in both axillae. The robot was docked after a working space was created through the port incision. Robotic thyroid resection was then performed.

Postoperative pain

To control postoperative pain, intravenous patient controlled analgesia (PCA; Automed 3300, AceMedical Co., Seoul, Korea) was used to administer fentanyl. The mode of PCA was a continuous infusion of 0.2 μg/kg/hr with boluses of 0.2 μg/kg and a lockout interval of 15 minutes (total regimen 100 mL). A subjective visual analogue scale (VAS) was used for patients to express pain intensity. All patients were preoperatively educated on the use of the VAS (0, no pain; 100, worst imaginable pain). The patients were instructed to push the button for PCA whenever they felt pain. If any expressed prolonged pain of over 40 mm on the VAS, they were given an intravenous injection of 50-μg fentanyl as rescue analgesia until the pain was relieved to a level falling below a VAS pain score of 40 mm. The patients were asked to describe the site at which pain was maximally felt.

Outcome measures

The primary outcome measure of the study was VAS pain score. The VAS pain scores were measured at 2, 6, 18, 30, 42, and 66 hours after surgery. The bottom hit counts (BHC) from PCA and fentanyl consumption (the sum of additional intravenous fentanyl bolus injections and the fentanyl delivered by the PCA system) were evaluated at similar time points: up to 2 hours, 2–6 hours, 6–18 hours, 18–30 hours, and 30–42 hours. CRP levels were checked at 2, 18, 42, and 66 hours after surgery. Mean blood pressure (BP) and heart rate (HR) were recorded at baseline, when the patients entered the recovery room, and when they exited the recovery room after surgery. The frequencies of postoperative nausea and vomiting (PONV) treated with intravenous ondansetron (4 mg) were recorded. Parameters such as drainage amount and hospital stay were also collected.

Statistical analysis

A pilot study was conducted measuring the VAS pain scores in 10 patients who received normal saline in order estimate the group sizes necessary for the main study. The mean and standard deviation of VAS pain scores at 2 and 66 hours after surgery was 45.2 ± 9.8 and 16.9 ± 6.4. The autocorrelation between adjacent measurements for the same subject was 0.6. For our power calculations, we assumed that first-order autocorrelation adequately represented the autocorrelation pattern. We wanted to be able to show 20% differences in VAS pain scores between groups. Therefore, for an α of 0.05 and a power of 80%, we needed 17 patients per group.

The Shapiro-Wilk test was used to test for normality of variables. For intergroup comparisons, the distribution of the data was first evaluated for normality using the Shapiro-Wilk test. Normally distributed data are presented here as the mean ± standard deviation and groups were compared by Student t test. Nonnormally distributed data are expressed as medians (P_{25}–P_{75}) and were analyzed using the Mann-Whitney U test.

As VAS pain score and fentanyl consumption were both nor-

Table 1. Demographic data

Variable	Group C (n = 17)	Group L (n = 17)	P-value
Age (yr)	34.7 ± 7.6	38.0 ± 10.1	0.292
Body mass index (kg/m^2)	21.8 ± 2.7	22.1 ± 2.3	0.680
Tumor size (cm)	0.7 (0.4–1.6)	0.6 (0.4–0.8)	0.377[a]
Operation type			0.831
Total thyroidectomy with CND	13 (76.5)	14 (82.4)	
Lobectomy with CND	2 (11.8)	2 (11.8)	
Lobectomy alone	2 (11.8)	1 (5.9)	
Operation time (min)	192.4 ± 30.9	210.5 ± 29.4	0.087
Pathology			>0.999
Papillary thyroid carcinoma	15 (88.2)	16 (94.1)	
Follicular adenoma	2 (11.8)	1 (5.9)	
Presence of extrathyroidal extension	2 (11.8)	5 (29.4)	0.398
No. of retrieved lymph nodes	7.0 (3.0–11.0)	4.0 (2.25–11.75)	0.859[a]
No. of metastatic lymph nodes	0 (0–3.0)	0 (0–1.0)	0.274[a]

Value are presented as mean ± standard deviation, median (P_{25}–P_{75}) or number (%).
Group C, saline infiltration group; group L, 0.1% ropivacaine infiltration group; CND, central neck dissection.
[a]Mann-Whitney U test was used and expressed as median (P_{25}–P_{75}) because of abnormal distribution.

mally distributed, they were compared by repeated measures analysis of variance (ANOVA) (Geisser-Greenhouse corrected F test) followed by Tukey test for multiple comparisons. As BHC and CRP were abnormally distributed, Friedman repeated-measures ANOVA was used to evaluate differences, followed by Tukey test for multiple pairwise comparisons.

Descriptive variables were subjected to chi-square analysis or Fisher exact test, as appropriate. P-values of 0.05 or less were considered statistically significant. Statistical analyses were performed using PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA).

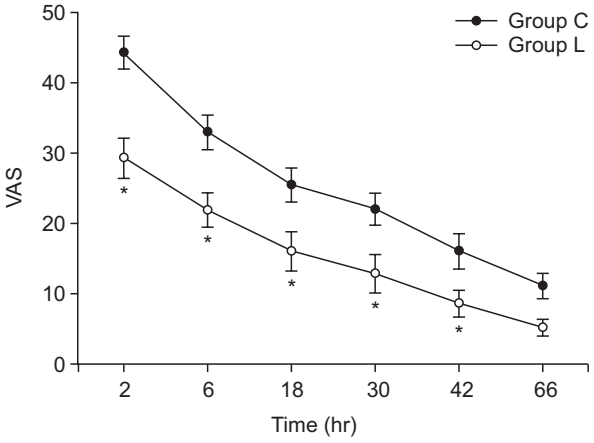

Fig. 2. Postoperative pain scores were lower in the ropivacaine group than in the control group after robotic thyroidectomy using bilateral axillo-breast approach. Values are expressed as mean ± standard error. Group C, saline infiltration group; group L, 0.1% ropivacaine infiltration group; VAS, visual analogue scale. *P < 0.05 compared with group C.

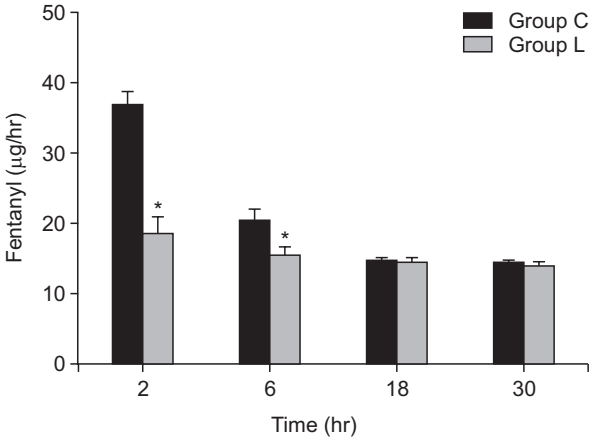

Fig. 3. Additional fentanyl use was lower in the ropivacaine group than in the control group at postoperative 2 and 6 hours. Values are expressed as mean ± standard error. Group C, saline infiltration group; group L, 0.1% ropivacaine infiltration group. *P < 0.05 compared with group C.

RESULTS

There were no differences between groups in terms of age, body mass index (BMI), tumor size, operation time, presence of extrathyroidal extension, the number of retrieved and metastatic lymph nodes (Table 1).

Although we administered postoperative PCA and rescue analgesia, some patients reported VAS pain scores greater than 40 mm during the immediate postoperative period. These VAS pain scores were recorded, and each patient was given an additional injection of fentanyl. In both groups, the pain levels were highest during the earliest period of observation and showed a tendency to diminish gradually. VAS pain scores were significantly lower in group L than in group C from 2 to 42 hours (Fig. 2).

The sites of pain felt by patients were divided into three regions: flap site pain, inner throat pain, and incision site pain. About 76.5% of the patients complained mostly of flap site pain (26/34 patients), while 17.6% patients complained of inner throat pain (6/34 patients) and 5.9% complained of incision site

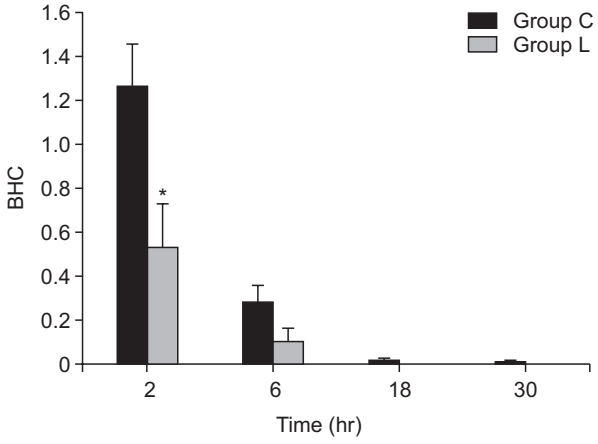

Fig. 4. The frequency bottom hit counts (BHC) were lower in the ropivacaine group than in the control group at postoperative 2 hours. Values are expressed as mean ± standard error. Group C, saline infiltration group; group L, 0.1% ropivacaine infiltration group. *P < 0.05 compared with group C.

Table 2. Total fentanyl consumption and BHC

	Group C	Group L	P-value
Fentanyl (μg)	510.75 (452.00–526.00)	422.50 (363.38–492.19)	0.009
BHC (n)	4.00 (3.00–5.00)	0 (0–2.50)	0.003

BHC, bottom hit counts; group C, saline infiltration group; group L, 0.1% ropivacaine infiltration group.
Mann-Whitney U test was used and expressed as median (P_{25}–P_{75}) because of abnormal distribution.

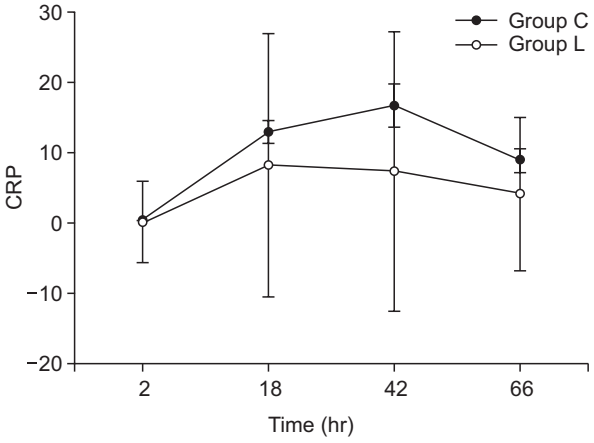

Fig. 5. The postoperative CRP levels were not significantly different between the two groups. group C, saline infiltration group; group L, 0.1% ropivacaine infiltration group. Values are expressed as mean ± standard error.

pain (2/34 patients). However, these pain sites were not clearly separated but were often ambiguously combined.

Fentanyl use for analgesia and BHC was significantly lower in group L than in group C during the first postoperative 6 and 2 hours, respectively (Figs. 3 and 4). The clinical differences between the two groups gradually diminished over time. The total fentanyl consumption and total BHC were lower in group L than group C (Table 2). The postoperative CRP levels were not statistically significant between the two groups (Fig. 5). No significant differences were noted for baseline and postoperative mean BP and HR. There were no significant differences between the two groups in postoperative drainage amount, the length of hospital stay, or complications such as PONV (Table 3).

Table 3. Operative outcomes

Variable	Group C (n = 17)	Group L (n = 17)	P-value
Baseline			
BP (mmHg)	79.2 ± 7.6	78.4 ± 7.2	0.759
HR (bpm)	73.2 ± 5.3	70.1 ± 9.0	0.219
Entry to recovery room			
BP (mmHg)	92.9 ± 11.1	92.5 ± 12.9	0.931
HR (bpm)	96.6 ± 11.6	92.6 ± 14.3	0.396
Exit to recovery room			
BP (mmHg)	92.9 ± 10.0	93.7 ± 11.8	0.834
HR (bpm)	86.9 ± 7.9	83.2 ± 11.0	0.288
Drainage amount (mL)	232.1 ± 68.8	230.6 ± 53.1	0.949
Hospital days	4.0 (4.0–4.5)	4.0 (4.0–4.0)	0.696[a]
PONV	2 (11.8)	2 (11.8)	1.000

Value are presented as mean ± standard deviation, median (P_{25}–P_{75}) or number (%).
Group C, saline infiltration group; group L, 0.1% ropivacaine infiltration group; BP, blood pressure; HR, heart rate; POVN, postoperative nausea and vomiting.
[a]Mann-Whitney U test was used and expressed as median (P_{25}–P_{75}) because of abnormal distribution.

DISCUSSION

Preemptive analgesia is a treatment that involves the introduction of an analgesic regimen before the onset of noxious stimuli, with the goal of preventing sensitization of the nervous system to subsequent stimuli that could amplify pain. There are many preemptive analgesia strategies such as local infiltration of anesthetics, nerve block, epidural block, subarachnoid block, intravenous analgesics and anti-inflammatory drugs [12-14]. We used infiltration with long-acting local anesthetic ropivacaine after administering general anesthesia and before incision to prevent peripheral sensitization and reduce postoperative pain. Previous studies showed that preoperative local infiltration of anesthetics to surgical sites was effective for reducing pain in patients undergoing open thyroidectomy [15]. Unlike open thyroidectomy, the flap lesion in robotic thyroidectomy using BABA extends to below the clavicle and is wider bilaterally. In our study, ropivacaine infiltration during robot thyroidectomy covered all flap sites beyond the incision site. We hoped that this procedure would block peripheral sensitization of all flap lesions.

Ong et al. [16] noted that preemptive local anesthetic infiltration improved analgesic consumption and time to first rescue analgesic request, but not postoperative pain scores in a meta-analysis. However our data showed lower pain scores as well as lower analgesic consumption in patients who received infiltration with local anesthetics. We hypothesized that the effects of local anesthetic infiltration could differ according to surgical procedure type, dose, and type of local anesthetic used. The meta-analysis by Ong et al. [16] included a variety of procedures such as laparoscopy, abdominal surgery, and orthopedic surgery. Shin et al. [17] showed that preoperative bilateral superficial cervical plexus block and ropivacaine wound infiltration were more effective for reducing pain scores than ropivacaine wound infiltration alone in patients undergoing robotic thyroidectomy. The doses and sites of ropivacaine infiltration by Shin et al. [17] were different from those in our study design. They also used 20 mL of 0.525% ropivacaine and only injected into the incision site, while we used 3 mg/kg of 0.1% ropivacaine with saline and injected into the whole flap site. These differences may have influenced the degree and duration of pain reduction.

Ropivacaine was chosen for this study because of it has a very long block duration, a greater margin of safety, and reduced toxic potential compared to bupivacaine [18]. We used 3 mg/kg, which is a high dose of ropivacaine but within the safe range, for which Kuthiala and Chaudhary [19] recommended

an infiltration dose of 7.5–225 mg. There were no side effects associated with ropivacaine infiltration. Although one patient complained of nausea and dizziness, it is not certain whether these symptoms were caused by ropivacaine infiltration or by other drugs such as fentanyl. Typically, thyroidectomy and general anesthesia are associated with PONV [20].

The duration of ropivacaine for peripheral nerve blocks is approximately 10–17 hours [18]. Our data indicated longer durations of blocks, lasting until postoperative 42 hours. We hypothesized that the preemptive effect could cause the duration to be longer than the drug itself. Some previous studies reported that local anesthetic infiltration for postoperative pain lasted only a short time [21-23]. On the other hand, Tverskoy et al. [24] and Pappas-Gogos et al. [25] reported pain reducing effects after local anesthetic infiltration lasting until postoperative 48 hours. The duration of pain reduction, as a preemptive effect, varied according to operation type and anesthetic method.

Shin et al. [17] reported that mean BP in patients treated with preoperative local infiltration was lower than in patients treated with saline infiltration in robotic thyroidectomy. Loggia et al. [26] noted that HR predicted pain in response to heat stimuli. We considered the use of objective parameters such as HR and BP to assess pain. However, our data did not show significant differences in these parameters between our two study groups, although BP and HR were increased in both after surgery. Some previous studies indicate that there are no truly objective pain markers, because pain is more than just the peripheral and spinal transmission of nociceptive information. According to these studies, HR is not strongly correlated with pain [27,28].

There were some limitations in this study. Our sample was small, and this was a single institute study. Although pain sites were partially separated, the evaluations of these sites were not separated because many patients complained of overall pain at the operation site, not pinpoint sites. The study was not performed in male patients because males are less likely to be diagnosed with thyroid cancer, and the number of male patients who desired robotic thyroidectomy was less than the number of females. The effect of local anesthetic infiltration in male patients remains unknown because response to pain differs between genders [29].

In conclusion, preoperative infiltration with ropivacaine to all flap sites at a dose of 3 mg/kg and at a concentration of 0.1% with saline is safe and effective for reducing postoperative pain and postoperative fentanyl consumption in patients undergoing robotic thyroidectomy.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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