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Preoperative flap-site injection with ropivacaine and epinephrine in BABA robotic and endoscopic thyroidectomy safely reduces postoperative pain

A CONSORT-compliant double-blinded randomized controlled study (PAIN-BREKOR trial)

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Abstract

Background: Clinical trials on bilateral axillo-breast approach (BABA) thyroidectomy show that levobupivacaine and ropivacaine significantly reduce postoperative pain, but they focused on BABA robotic thyroidectomy only and did not identify specific sites of significant pain relief. Our objective was to assess the pain reduction at various sites and safety of ropivacaine-epinephrine flap injection in BABA thyroidectomy.

Methods: This prospective double-blinded randomized controlled trial was conducted in compliance with the revised CONSORT statement (ClinicalTrials.gov registration no. NCT02112370). Patients were randomized into the ropivacaine-epinephrine arm or control (normal saline) arm.

Results: From January 2014 to May 2016, 148 patients participated. The primary endpoint was site-specific pain, as measured by numeric rating scale 12 hours after surgery. The ropivacaine-epinephrine group exhibited significantly less swallowing difficulty ($P = .008$), anterior neck pain ($P = .016$), and right ($P = .019$) and left ($P = .035$) chest pain. Secondary endpoints were systolic ($P = .402$), diastolic ($P = .827$) blood pressure, and pulse rate ($P = .397$) after injection before incision and during surgery. The vital signs of the groups just after injection did not differ. During surgery, the ropivacaine-epinephrine patients had higher pulse rates (99 ± 13.3 vs 88 ± 16.1, $P < .001$) but within normal range. There were no adverse events such as postoperative nausea and vomiting. There was no significant difference in pain scores in either patient group between patients who underwent robotic or endoscopic interventions.

Conclusion: BABA flap-site injection with ropivacaine and epinephrine mix before incision effectively and safely reduced postoperative pain. Future studies should focus on tailoring ropivacaine and epinephrine dosage for individuals.

Abbreviations: BABA = bilateral axillo-breast approach, NRS = numerical rating scale, PCA = patient-controlled analgesia, PONV = postoperative nausea and vomiting, TSH = thyroid-stimulating hormone, TAA = transaxillary approach.

Keywords: bilateral axillo-breast approach, pain, thyroidectomy

1. Introduction

Minimally invasive thyroid surgery was first introduced in 1996 by Gagner,[1] after which several different methods were developed.[2–4] In particular, the incorporation of the da Vinci Robot System (Intuitive Surgical, Inc., Mountain View, CA) has further accentuated the advantages of minimally invasive thyroidectomy relative to conventional open thyroidectomy,

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namely, its superior postoperative cosmetic outcomes, lower complication rates, and faster recovery.[5–8] However, patients who undergo minimally invasive thyroidectomy are more likely than patients undergoing the open procedure to experience immediate postoperative pain; this is primarily due to the flap dissection that is required to establish an adequate operative field.[9,10]

Five prospective randomized controlled studies have taken a variety of measures to reduce pain in minimally invasive thyroid surgery.[11–15] Three of them focused on thyroidectomy with the bilateral axillo-breast approach (BABA) and the effect of local infiltration of the flap site with the anesthetic agent levobupivacaine[14] and ropivacaine.[13,15] These agents were administered either as spray[14,15] or as a subcutaneous injection.[13] All studies found that they significantly reduced pain. However, it was not stated how the anesthetic agents improved pain at specific locations, and potential drug interactions with epinephrine (commonly used to reduce bleeding from flap sites) were not addressed. Moreover, these studies only included patients who underwent BABA robotic thyroidectomy; patients who underwent BABA endoscopic thyroidectomy were excluded.

To address these issues, we performed a double-blinded, randomized, placebo-controlled trial to evaluate the efficacy of preoperative injection of the skin flap with a mixture of ropivacaine and epinephrine in patients who underwent either BABA robotic or BABA endoscopic thyroidectomy. Pain at specific sites 12 hours after the operation was measured using a numerical rating scale (NRS). Moreover, the effect of the treatment on vital signs during the operation was assessed. We hypothesized that injecting ropivacaine-epinephrine mixture at flap site before dissection in BABA thyroidectomy would effectively decrease immediate postoperative pain at specific sites without inducing any vital sign instability.

2. Methods

This randomized controlled study was performed at our institution, situated in Seongnam-si, Gyeonggi-do, South Korea. It was approved by the Institutional Review Board of our hospital (Approval No. B-1403/242-006) and was registered on the ClinicalTrials.gov database (No. NCT02112370). The study protocol was in compliance with the revised CONSORT statement for reporting randomized trials,[16] and the trial was conducted according to the Declaration of Helsinki and all its revisions. All patients provided written informed consent to participate in the trial.

2.1. Participants

All patients referred for BABA robotic or endoscopic thyroidectomy in our hospital between January 5, 2014, and May 5, 2016, were candidates for inclusion. Patients who would undergo completion thyroidectomy and/or modified radical neck dissection were excluded as well as patients who had a history of allergy or hypersensitivity to local anesthetics, stroke, uncontrolled hypertension or diabetes, coagulopathy, and/or severe cardiovascular or pulmonary renal disease. Patients who could not communicate in Korean well enough to understand the NRS pain score questionnaires were also excluded.

2.2. Randomization and blinding

On the day before the operation, the participants were randomized to be injected with either a mixture of ropivacaine and epinephrine or normal saline only. The randomized sequence was generated by a statistician who was not involved in this study using software PASS 11 (NCSS, Kaysville, UT). The size of the randomization block was 4, and the distribution ratio to each arm was set at 1:1. The code was kept secure by an uninvolved physician assistant who informed the scrub nurse which fluid to prepare before the operation. The involved surgeons, NRS score assessor, and patients were blinded to the treatment allocation for the duration of the study: only the physician assistant and the scrub nurse were aware of the treatment assignment.

2.3. Intervention and protocol

The procedure of BABA thyroidectomy has been well described in previous studies.[13–15,17] In brief, the patients were placed on a specially designed pillow in the supine position with the neck extended. After marking the skin flaps, the fluid chosen on the basis of the randomization sequence was injected into the subcutaneous layer of the flap site for hydrodissection. The ropivacaine-epinephrine group received 225 mg of ropivacaine and epinephrine 1 mg/1 mL diluted by 1:100,000 that was mixed with 100 mL of normal saline. The control group received 100 mL of normal saline alone. The flap was raised, and the bilateral axillary and circumareolar ports (8–12 mm for robotic surgery and 5–12 mm for endoscopic surgery) were inserted. The working space was then insufflated with carbon dioxide gas at a pressure of 6 mm Hg through the 12 or 5 mm camera port. The operation was performed by 3 experienced surgeons who had at least 4 or more years of experience in BABA thyroidectomy from the same institution. No type of patient-controlled analgesia (PCA) was used because this was already the routine procedure for this surgery. It also ensured a more accurate reflection of the NRS scores on patient pain. However, on patient demand, intravenous injections of fentanyl (50 μg) were administered during the first hour in the recovery room, and ketorolac in vials (15 mg per vial) was intravenously injected only on demand after the patients had been transferred to the ward. No other types of pain-killers were administered to the participants.

2.4. Outcomes

The primary endpoint was the NRS pain score at 6 specific areas of the body 12 hours after operation. The pain score ranged from 0 (no pain at all) to 10 (the most intense pain imaginable). The areas of the body assessed were as follows: the throat (expressed as swallowing difficulty), anterior neck, right chest, left chest, posterior neck, and back (Fig. 1). Postop 12 hours was specifically chosen because it is the night after the operation, when patients are more sensitive to pain.

Secondary outcomes were degree of vital sign fluctuation just after the injection but before the first incision, (degree of vital sign fluctuation during the operation, the general NRS pain score 0, 1, 2, 4, 6, 9, 12, 24, and 48 hours after the operation, the frequency of analgesic administration 0, 1, 2, 4, 6, 9, 12, 24, and 48 hours after the operation, the operation time and estimated blood loss of both groups (to assess vasoconstrictive effects of epinephrine in facilitating the operation), frequency of postoperative nausea and vomiting (PONV) complaints during hospitalization, and (vii) a subgroup analysis of specific NRS pain scores of robotic and endoscopic recipients in both treatment arms. The general NRS was defined as the overall pain felt by the patient rather than that at a specific site.

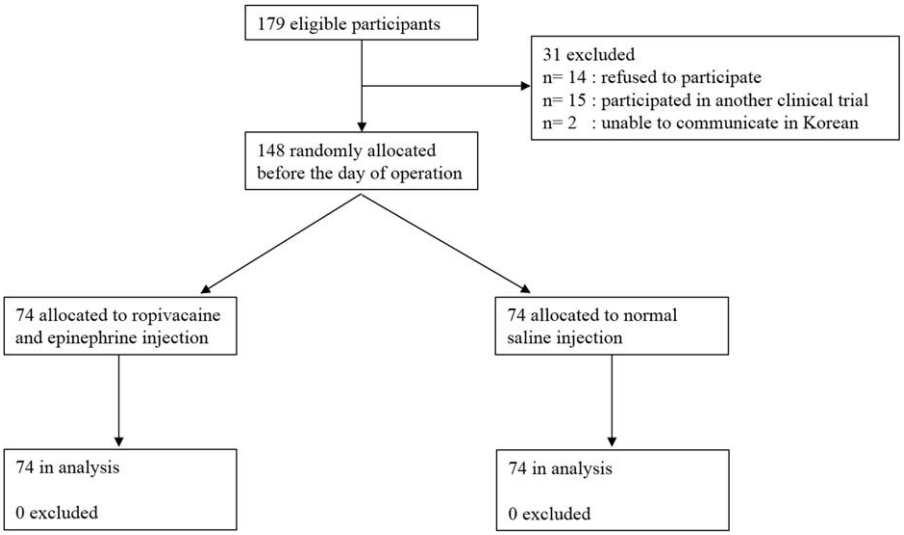

Figure 1. Flow diagram of patient enrollment.

2.5. Determination of the sample size and statistical methods

To calculate the necessary sample size, we employed data from a randomized controlled study recording total opioid requirement of 41 patients who underwent vaginal hysterectomy with and without ropivacaine injection,[18] because publication on ropivacaine use on BABA flap was lacking at protocol conception of this study. Setting the α error to 0.05 and the power to 80% to detect statistical significance ($P = .05$, two-tailed), each arm required at least 67 patients. Assuming a drop-out rate of 10%, we estimated that 148 patients (74 in each arm) would be required.

All data analyses were performed according to a pre-established statistical analysis plan. Continuous variables were presented as means and standard deviation, and categorical data were presented as numbers and proportions. The ropivacaine-epinephrine and control groups were compared in terms of these variables using Student *t* test and Fisher exact test, respectively. All statistical analyses were performed using R.3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).[19] The graph was generated using the same program. A *P* value of $< .05$ was considered to indicate statistical significance.

3. Results

Between January 2014 and May 2016, 179 patients underwent BABA thyroidectomy at our institution. All were asked to participate in the trial. Of these patients, 148 agreed and 31 refused (Fig. 2). All participants were hospitalized and randomized the day before the operation. None of the patients dropped out before the end of the trial (i.e., 48 hours after surgery) and were analyzed for the primary and secondary outcomes.

The baseline demographic and clinicopathological characteristics of the patients are summarized in Table 1. There were 74 patients in both the ropivacaine-epinephrine and control groups. Although the ropivacaine-epinephrine group had significantly higher preoperative thyroid-stimulating hormone (TSH) levels

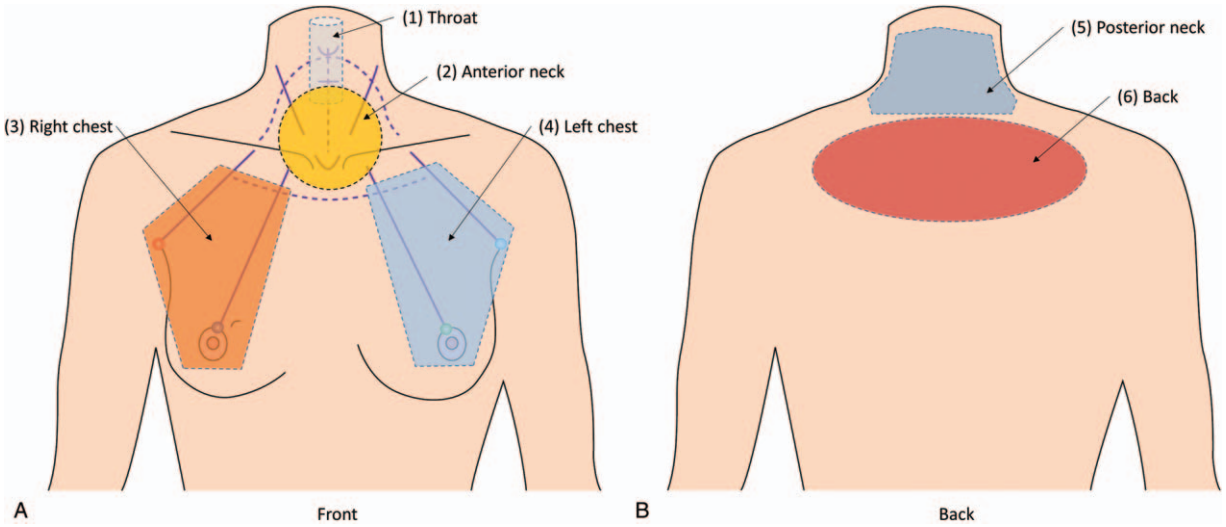

Figure 2. Diagram of specific sites of pain assessment at 12 hours post-operation.

Table 1

Baseline demographic and clinicopathologic characteristics.

Characteristics	R/E (n = 74)	NS (n = 74)	*P*
Demographic			
Gender			.563
Male	8	5	
Female	66	69	
Mean age, y	35.5 ± 8.8	38.0 ± 9.3	.104
Body mass index, kg/m^2	23.3 ± 4.0	22.9 ± 2.5	.449
Preoperative thyroid function test			
T3, ng/dL	123.3 ± 25.1	121.8 ± 15.0	.654
Free T4, ng/dL	1.2 ± 0.4	1.2 ± 0.3	.481
TSH, ulU/mL	2.2 ± 1.7	1.8 ± 1.0	**.042**
Operative results			
Method			.853
Robotic	55	53	
Endoscopic	19	21	
Extent			.780
Right	29	26	
Left	24	28	
Total	21	20	
Duration, min	155.3 ± 46.8	163.6 ± 54.1	.315
Estimated blood loss, mL	18.0 ± 40.5	30 ± 58.2	.134
Pathology			
Histology			.651
PTC	61	64	
Non-PTC	13	10	
Site			.419
Right	35	28	
Left	32	36	
Isthmus	1	4	
Combined	5	6	
Size, mm	11.2 ± 8.5	10.5 ± 9.3	.631
Multiplicity	1.3 ± 0.7	1.3 ± 0.6	.793
LN metastasis	1.0 ± 2.3	1.5 ± 2.8	.259
LN retrieved	4.3 ± 4.2	6.1 ± 7.1	.059

LN = lymph node, NS = normal saline (control), PTC = papillary thyroid carcinoma, R/E = ropivacaine-epinephrine, TSH = thyroid-stimulating hormone.
Bold font means: $P < .05$.

than the control group (2.2 ± 1.7 vs 1.8 ± 1.0, $P = .042$), both were within the normal range (0.3–4.0 IU/mL). Thus, this difference was not clinically significant. Moreover, the 2 groups had similar preoperative T3 (123.3 ± 25.1 vs 121.8 ± 15.0, $P = .654$) and free T4 (1.2 ± 0.4 *vs*. 1.2 ± 0.3, $P = .481$) values. Apart from the TSH level, none of the demographic, operative, and clinicopathologic results demonstrated statistically significant difference between the 2 arms.

The NRS pain score 12 hours postsurgery, which was the primary outcome of the trial, indicated that the use of ropivacaine-epinephrine significantly reduced postsurgical discomfort (Fig. 3.). Specifically, the use of ropivacaine-epinephrine significantly reduced swallowing difficulty ($P = .008$), anterior neck pain ($P = .016$), and right ($P = .019$) and left ($P = .035$) chest pain. However, ropivacaine-epinephrine did not significantly influence back pain ($P = .089$) or posterior neck pain ($P = .634$), perhaps because they were not the sites of injection.

Analysis of the intraoperative vital signs showed that the injection was safe: the ropivacaine-epinephrine and control groups did not differ significantly in terms of systolic ($P = .402$) and diastolic ($P = .827$) blood pressure and pulse rate ($P = .397$) immediately after the injection and just before the first incision. Analysis of the 2 groups in terms of the highest blood pressure and pulse rate observed during the operation showed that the ropivacaine-epinephrine group had a significantly higher pulse rate than the control group (99 ± 13.3 vs 88 ± 16.1, $P < .001$). However, both measurements were within normal limits. Moreover, the ropivacaine-epinephrine group patients had a significantly higher baseline pulse rate at admission than the control group (78 ± 11.4 vs 72 ± 11.2, $P = .002$) (Table 2).

General (whole body) NRS measurements at various time points over the first 48 hours after surgery showed that, in both groups, the intensity of pain decreased as time passed. This was also true in terms of the usage of pain killers. The ropivacaine-epinephrine group tended to have lower NRS pain scores and to use fewer pain killers than the control group, although this trend did not achieve statistical significance at any time point (Table 3).

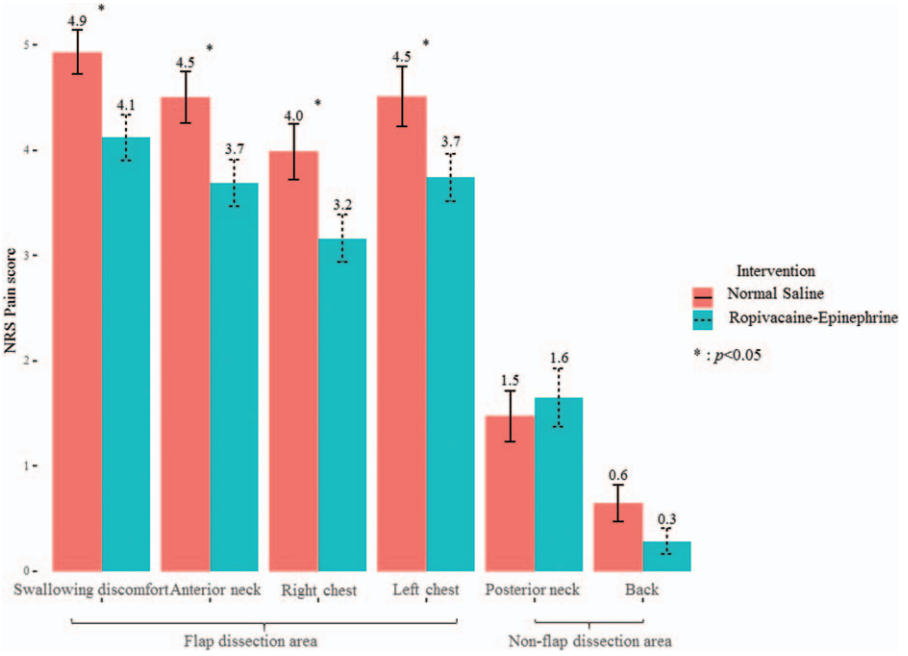

Figure 3. Pain numeric rating scale at 12 hours postoperation.

Table 2

Vital sign stability before and during operation.

Parameters	R/E	NS	P
At admission			
Systolic BP	123 ± 12.6	120 ± 12.7	.134
Diastolic BP	75 ± 10.9	72 ± 10.7	.240
PR	78 ± 11.4	72 ± 11.2	**.0.02**
Preincision			
Systolic BP	118 ± 17.7	115 ± 22.5	.402
Diastolic BP	68 ± 14.6	68 ± 15.4	.827
PR	79 ± 13.2	77 ± 13.1	.397
Highest intra op			
Systolic BP	145 ± 18.9	142 ± 16.5	.265
Diastolic BP	86 ± 19.2	91 ± 14.9	.077
PR	99 ± 13.3	88 ± 16.1	**<.001**

BP = blood pressure, NS = normal saline (control), PR = pulse rate, R/E = ropivacaine-epinephrine. Bold font means: $P < .05$.

There were 7 (9.5%) and 5 (6.8%) patients who did not request additional pain-killers at the ward in the ropivacaine-epinephrine group and the control group, respectively.

The operation took 155.3 ± 46.8 minutes in the ropivacaine-epinephrine group and 163.6 ± 54.1 minutes in the control group ($P = .315$), and estimated blood losses were 18.0 ± 40.5 and 30 ± 58.2 mL ($P = .134$), respectively (Table 1). None of the participants exhibited anesthesia- and/or drug injection related adverse events during or after the operation such as PONV.

Finally, the subgroup analysis of specific NRS pain scores indicated minimal differences between robotic and endoscopic patients in both treatment arms. In the ropivacaine-epinephrine arm, the posterior neck pain score was 2.0 ± 2.6 for robotic patients versus 0.7 ± 1.5 ($P = .016$) for endoscopic patients, while in the control arm, left chest pain score was 5.0 ± 2.3 for robotic patients versus 3.2 ± 2.4 for endoscopic patients ($P = .004$). Other areas showed no differences in pain scores between the 2 arms (data not shown).

4. Discussion

The NRS pain scores and vital sign measurements in both arms of our trial support the hypothesis that injecting the flap with a mixture of ropivacaine and epinephrine before incision safely reduces postoperative regional pain 12 hours after BABA thyroidectomy. Furthermore, we identified the specific areas in which the injection significantly reduced pain and discomfort: they were the throat, anterior neck, and left and right chest areas. All of these sites are directly involved in the formation of the flap in BABA thyroidectomy. Although the general NRS pain scores and analgesic consumption demonstrated a consistent pattern of less pain and pain killer administration in the ropivacaine-epinephrine arm compared with the control arm at each point of postoperative observation time, these differences between the 2 groups did not achieve statistical significance.

The meta-analysis of Ong et al[20] showed that, although preoperative local anesthetic infiltration effectively reduces postoperative analgesic administration, it does not lower postoperative pain scores. However, thyroidectomies were not included in that analysis. A randomized controlled trial published afterwards showed that, in conventional open thyroidectomy, preoperative surgical site injection with local anesthetics effectively reduced pain.[21] This was also observed for the 2 predominant minimally invasive thyroidectomy approaches in the field, namely, the transaxillary approach (TAA) and BABA. Kim et al[12] and Shin et al[11] showed that the delivery of analgesics through various procedures effectively reduced postoperative pain after TAA. Similar findings were reported by the 3 randomized trials on BABA. The trial of Ryu et al[14] with 58 patients showed that 0.25% levobupivacaine spray on the flap site after the operation yielded lower NRS scores and PCA consumption 1, 6, 24, and 48 hours after surgery. They also mentioned that the neck and anterior chest was the most painful site after surgery. The second trial by Kang et al[13] enrolled 34 women and showed that preoperative ropivacaine injection of the flap site reduced the pain score, PCA consumption, and additional analgesic requirement at 2, 6, 18, 30, 42, and 66 hours after surgery. The sites of pain were not noted. Most recently, Bae et al[15] showed with a cohort of 108 patients that ropivacaine spray of the flap after the operation reduced the pain scores and analgesia consumption 1, 2, 4, 8, 16, and 24 hours after the operation. They graded the severity of PONV but found that ropivacaine did not affect its distribution in the study and control groups.

In our trial, we chose preoperative injection rather than postoperative spray as the method of drug delivery not only because most of the spray tends to drain out postoperatively, but also because local infiltration is proven to be effective in reducing pain in open and robotic thyroidectomy.[13,22] We also chose ropivacaine as our local anesthetic because of its long block duration, lower toxicity than levobupivacaine, and greater safety.[23] Its low lipophilic profile also means that it is unlikely to induce cardio- and central nervous system toxicity.[24–26] Moreover, many clinical trials on postoperative, labor, and intrathecal pain have demonstrated that it is both effective and has few adverse outcomes. In addition, the clinical trials of Kang et al[13] and Bae et al[15] that were mentioned above demonstrated that it effectively reduces pain after BABA thyroidectomy. Our trial differs from the latter 2 studies in that we mixed ropivacaine

Table 3

Change in NRS score and pain killer usage with time.

Post op time, h	0	1	2	4	6	9	12	24	48
NRS pain score									
R/E	5.68	4.7	4.11	3.34	3.28	3.14	3.18	2.95	2.08
NS	5.73	4.05	4.55	3.55	3.39	3.28	3.19	2.93	2.27
P	.874	.232	.109	.287	.602	.507	.950	.939	.214
Pain killer administration (number of administrations)									
R/E	0.84	0.31	0.26	0.11	0.15	0.12	0.19	0.16	0.07
NS	1	0.35	0.31	0.07	0.18	0.14	0.18	0.2	0.01
P	.139	.614	.483	.387	.658	.807	.846	.560	.097

NS = normal saline (control), NRS = Numerical rating scale, R/E = ropivacaine-epinephrine.

with epinephrine. This decision was based on a study that showed that a mixture of ropivacaine and epinephrine significantly and safely reduces postoperative pain in cesarean section patients.[27] Epinephrine is frequently used in hydro-dissection during BABA to reduce bleeding during flap formation. This reflects its ability to induce peripheral vasoconstriction and yield a spotless flap. By contrast, when epinephrine is not used, the flap is likely to be diffusely tinged with blood. Notably, we found that the use of epinephrine reduced the estimated blood loss (18.0 vs 30 mL) and operation time (155.3 vs 163.6 minutes) in the ropivacaine-epinephrine group. Although these differences did not achieve statistical significance, they suggest that injecting the flap with epinephrine before surgery could aid the procedure of BABA thyroidectomy. Moreover, the higher maximum intraoperative pulse rate of the epinephrine group is not likely to cause clinically significant outcome because it was contained within normal limits.

Another noticeable difference between our trial compared and previous trials is that all BABA procedures, both robotic and endoscopic, were included: by contrast, all 3 previous trials only included patients who underwent robotic BABA. The 2 procedures are virtually the same in procedure, the only difference being the docking of the robot and the size of the port insertion sites (8 and 12 mm for the robotic procedure vs 5 and 12 mm for the endoscopic procedure), but the robotic procedure is 4 times more expensive for the patients under the Korean national insurance system. Our subgroup analysis demonstrated minimal NRS pain score differences between robotic and endoscopic patients in each treatment arm so that effect of ropivacaine and epinephrine injection may be presumed similar in both BABA robotic and endoscopic thyroidectomy patients. This statement should be validated, however, with additional patients in both subgroups designed to address the statistical significance.

Our study was also unique in that we did not use any kind of PCA. This probably explains why there were no adverse events such as PONV, headaches, or dizziness. Although many institutions routinely use PCA for patients undergoing BABA robotic thyroidectomy, it has been our policy not to use it even before the start of this trial because of the frequent incidence of PONV. This policy is now supported by our result that shows preoperative ropivacaine and epinephrine injection effectively controls postoperative pain, thus allowing PCA to be avoided and thereby reducing the incidence of PONV and other minor adverse events.

Of importance from our result is the inconsistency in postoperative 12-hour regional NRS and general NRS outcomes between the 2 arms. In BABA thyroidectomy, most of the postoperative pain is caused by the flap dissection procedure. Consequently, this is the main target for reducing postoperative pain. However, nonspecific and trivial factors such as soreness after long bed rest may also result in higher pain scores and analgesic consumption. We addressed this issue separately by measuring the pain that was felt at exact locations: our results show that ropivacaine specifically alleviated pain in the injected flap area but had no effect on the pain in nearby but uninvolved areas. In this context, our postoperative 12-hour general NRS score revealing a different result from the site-specific 12-hour NRS scores emphasize the importance of dealing general postoperative pain and pain due to flap dissection as 2 separate entities.

There are, however, some study limitations. Most importantly, it was a single-institution study, which may limit the generalizability of our results to other settings. Moreover, our institution is located in an affluent area compared with many other neighborhoods in our country. This suggests that our patient group was more likely to have a higher socioeconomic status than that of other patients undergoing thyroidectomy elsewhere in South Korea. However, given the nature of Korean insurance policy, in which costs are higher for minimally invasive operations, it is likely that those with higher socioeconomic status will receive BABA thyroidectomy. In addition, because this study was the first to mix ropivacaine and epinephrine in the injection, we set a variety of comorbid medical conditions as contraindications for the injection: the aim was to prevent the development of severe adverse events to the injection, although none of the participants met the exclusion criteria. Similarly, the 3 randomized controlled studies on BABA thyroidectomy set similar exclusion criteria. Notably, the mean ages of the patients in these 3 studies were 42, 40, and 36 years, which is comparable to the mean age (37 years) of our cohort. Our study together with the results of previous trials suggest that patients of high socioeconomic status in their 30s to 50s and lacking comorbid medical conditions are likely to be potential candidates for BABA thyroidectomy. Thus, when seen in the context of the results of previous studies, our results seem generalizable to this subgroup of patients. However, external validation of our protocol would be ideal.

The second study limitation was that we did not directly examine whether the vasoconstrictive properties of epinephrine helped to reduce bleeding and therefore resulted in a hemorrhage-free operative field; estimated blood loss and operation time are only indirect measures of this property of epinephrine. Future studies should employ more direct measurements of the usefulness of epinephrine; an example would be to employ bioengineering methods to measure how much red pigment there is on the screen.

Finally, the issue regarding the importance of the statistical versus the clinical significance of the pain score remains to be addressed. Our 12-hour pain results demonstrate statistical significance, by which we may interpret the effect to be real. According to a study by Younger et al,[28] a 2 point decrease in the NRS score may considered to be a "very much improved" reduction in pain. Does it mean that 1 point decrease in NRS score of our patients signify a "moderate improvement" in pain reduction? As pain is a subjective issue, however, that question is unlikely to be answered. Moreover, as a valid and reliable method of quantifying an individual's of pain objectively does not exist at the moment, the best way to achieve clinically significant pain reduction may be to utilize all measures that can safely and effectively reduce pain.

In conclusion, injecting a mixture of ropivacaine and epinephrine in the BABA flap site before incision safely and effectively reduces postoperative pain without causing postoperative complications such as PONV. By implementing this protocol, we expect patients to benefit from the cosmetic superiority of BABA thyroidectomy while circumventing its downside, postoperative pain. Future studies should focus on the individual tailoring of the ropivacaine and epinephrine dose on the basis of demographic variables such as dose per kilograms.

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