의학석사 학위논문

The effect of intraoperative nefopam administration on acute postoperative pain and chronic discomfort after robotic or endoscopic assisted thyroidectomy: A randomized clinical trial

내시경 혹은 로봇 갑상선 절제술 후 통증조절에 있어서 수술 중 정맥 주입한 nefopam의 효과

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The effect of intraoperative nefopam administration on acute postoperative pain and chronic discomfort after robotic or endoscopic assisted thyroidectomy: A randomized clinical trial

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Abstract

Background: Acute postoperative pain and chronic discomfort are reported after robotic or endoscopic thyroidectomy. The purpose of this prospective, randomized, and double-blinded clinical trial was to investigate whether intraoperative infusion of nefopam decreases acute postoperative pain and chronic discomfort following either a robotic or endoscopic thyroidectomy via the bilateral axillo-breast approach (BABA).

Methods: Patients were randomized into two groups: The control group (n = 29) or the nefopam group (n = 29). Patients in each group were infused with the same volume of saline or nefopam (0.2 mg/kg bolus, 120 μg/kg/h continuous infusion) during surgery. Acute postoperative pain, the need for rescue analgesics, and other postoperative adverse effects were assessed at 1, 6, 24, and 48 hours postoperatively. Chronic pain and discomfort was recorded at 3 months after surgery.

Results: Patients in the nefopam group reported lower pain scores in the neck, as well as the axilla and anterior chest areas at 1, 6, 24, and 48 hours postoperatively, when compared with the control group ($P < 0.05$ at each time points). Rescue analgesics were required less in the nefopam group than in the control group (1.4 [1] *vs.* 2.3 [1.5]; $P = 0.001$). The degree of chronic pain and discomfort were relatively lower in the nefopam group ($P < 0.05$).

Conclusion: We report that intravenous nefopam infusion during surgery

decreased acute postoperative pain and the need for rescue analgesics, as well as chronic discomfort, following BABA robotic or endoscopic thyroidectomy without adverse events.

Keywords: Acute pain, Chronic discomfort, Endoscopic thyroidectomy, Nefopam, Robotic thyroidectomy.

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INTRODUCTION

Robotic or endoscopic thyroidectomy has been widely adopted for the treatment of thyroid disease to satisfy patient's cosmetic outcome and to improve postoperative recovery. This remote approach from the neck has an advantage compared with the conventional, open thyroidectomy. That is, without sacrificing surgical and oncological safety profile, this remote approach is less invasive, leaving no scars on the anterior neck area.[1] However, it requires wide flap dissection and subcutaneous tunneling of the neck and anterior chest to ensure sufficient working space during surgery, which results in significant tension inside the flap due to insufflation of CO_2.[2] Thus, robotic or endoscopic thyroidectomy has been known to cause moderate to severe pain in the neck, anterior chest, and axillary area after surgery.[3, 4]

Postoperative pain may lead to marked discomfort, delayed recovery, decline in the quality of life, prolonged hospitalization, and development of chronic pain. Postoperative acute pain control is necessary to improve recovery profiles and to prevent chronic pain and sensory disturbances. Numerous pharmacologic methods have been investigated for acute pain control after robotic or endoscopic thyroidectomy. Nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids may be effective for postoperative analgesia. However, NSAIDs should be avoided due to possible increased risk of bleeding complications on the airway[5] and opioids may not be effective for thyroidectomy patients since postoperative nausea and vomiting (PONV) is common after thyroidectomy.[6] Several analgesic methods

have been evaluated with robotic or endoscopic thyroidectomy for the management of acute pain.[7-9] Perioperative intravenous paracetamol infusion was effective for pain management in patients with robot-assisted endoscopic thyroidectomy via the transaxillary approach,[7] but this required repeated administration over a 24-hour period. In another study, pregabalin 150 mg was administered twice perioperatively for patients with robot-assisted endoscopic thyroidectomy, and this was effective in reducing acute postoperative pain but not chronic pain.[8] It is noteworthy that pregabalin has been associated with some undesirable effects, such as sedation and dizziness.[8] Kim et al.,[9] suggested that intraoperative intravenous ketamine infusion resulted in lower postoperative pain scores following robotic or endoscopic thyroidectomy without major adverse events; however, chronic pain and discomfort was not assessed in their study.

Nefopam, derived from a non-sedative benzoxazocine, is a non-opioid, non-steroidal, and centrally acting analgesic drug.[10] Nefopam is often used to reduce postoperative pain, in a multimodal fashion, by inhibiting the reuptake of serotonin, norepinephrine, and dopamine.[10] It also has effects on the glutamatergic pathway via modulation of sodium channels and acts as N-methyl-D-aspartate (NMDA) receptor antagonist.[11] With these properties, nefopam can be considered to reduce acute postoperative pain and to prevent the development of chronic pain and sensory disturbances. However, to the best of our knowledge, the effects of perioperative nefopam infusion on postoperative acute and chronic sensory disturbances have not been evaluated after robotic or endoscopic thyroidectomy. It

was hypothesized that intravenous nefopam infusion during surgery could decrease not only acute postoperative pain, but also chronic pain and discomfort. Therefore, this randomized and controlled trial investigated the effects of intraoperative nefopam infusion on postoperative pain, rescue analgesics, recovery profiles, chronic pain, and discomfort in patients undergoing robotic or endoscopic thyroidectomy via bilateral axillary breast approach (BABA).

METHODS

Study

This prospective, randomized, and double-blinded controlled trial was approved by The Institutional Review Board of Seoul National University Bundang Hospital (B-1604-341-004), and the protocol was registered at http://cris.nih.go.kr (registration number KCT0001950).

Patients

Patients scheduled for elective BABA robotic or endoscopic thyroidectomy at Seoul National University Bundang Hospital, between June 2016 and January 2017, were recruited. All patients had signed the written informed consent during preoperative visit.

Inclusion criteria were American Society of Anesthesiologist physical status I or II, age between 19 and 69 years, and thyroid mass without evidence of extracapsular soft tissue invasion or metastasis. Exclusion criteria were as follows: (1) allergy or hypersensitivity of nefopam, (2) chronic use of opioids or any kind of analgesic drugs more than 2weeks before the surgery, (3) myocardial infarction, (4) angle closure glaucoma, (5) history of seizure, (6) current medication with monoamine oxidase inhibitors, (7) previous surgical history of chest or neck area, (8) Obesity, Body Mass Index (BMI) > 40 kg/m^2, (9) pregnancy or lactation, and

(10) urinary tract disease causing urinary retention.

Randomization and intervention

Randomization was performed before the induction of anesthesia by an anesthesiologist, who was only in charge of the randomization. According to a computer-generated random number table (Random Allocation Software Version 1.0) with a block size of 4, patients were assigned to either the control group (n = 29) or the nefopam group (n = 29). Patients, anesthesiologists responsible for the patients, and outcome assessors were blinded to the group assignment. Study solutions (normal saline or nefopam) were prepared by an anesthetic nurse and delivered to the operating room in identical 50 ml syringes to ensure blinding. Right after the induction of anesthesia, the nefopam group received 0.2 mg/kg of nefopam (Accupan®, Pharmbio Korea, Seoul, Korea) intravenously, and then 120 μg/kg/h continuous infusion until the end of the operation (skin closure), whereas patients in the control group received the same volume of normal saline over the same period.

Anesthesia

Patients received 0.03 mg/kg of midazolam intravenously for premedication at the reception area. On arrival at the operating room, standard monitoring, including

pulse oximetry, noninvasive arterial pressure, and electrocardiogram, were used with bispectral (BIS) index monitoring (A-2000 BISTM monitor; Aspect Medical Systems, Inc., Natick, MA, USA). Total intravenous anesthesia with propofol and remifentatnil was used with target controlled infusion (Orchestra®, Fresenius vial, Brezins, France). The dose of propofol was adjusted to maintain the BIS value within 40 to 60, and the remifentanil dose was titrated to maintain the arterial pressure and heart rate within the range of 80% to 120% of the baseline value. Rocuronium 0.6 mg/kg was given to facilitate tracheal intubation, and additional dose of rocuronium (0.15 mg/kg) was administered to keep the train-of-four (TOF) count to be 1 or 2 with a stimulation of the adductor pollicis muscle. Ventilation was made to maintain the end-tidal CO_2 ($EtCO_2$) between 35-40 mmHg with inspired fraction of oxygen 50%. At the end of surgery, neuromuscular blockade was reversed with neostigmine 0.04 mg/kg plus glycopyrrolate 0.01 mg/kg after confirming the TOF count $\geq$ 4. Patients were extubated when they were fully recovered, then transferred to the post anesthetic care unit (PACU).

Surgical technique

All robotic or endoscopic assisted thyroidectomy using BABA was performed by a single experienced surgeon to keep a constant surgical stimulus, as previously described.[12] Patients were in supine position, and a pillow was placed under the shoulder to enhance neck extension. Skin flaps were marked, and 200 ml of diluted epinephrine solution was injected subcutaneously over the subplatysmal space and

upper chest area. Bilateral circumareolar incisions were made at the superomedial margin of each areolar, with two 8 mm axillary incisions. The flap was dissected and extended to the thyroid cartilage superiorly, 3 cm below the clavicle inferiorly, and laterally, from just beyond the lateral border of one sternocleidomastoid muscle to the other. Gas insufflation to the working space was done with CO_2 gas, at a pressure of 5-6 mm Hg through the 12 mm port. Then, robotic or endoscopic devices were docked, and the midline was separated by a monopolar electrocautery until the thyroid was visible. Isthmus was separated using an ultrasonic shear after the identification of the cricothyroid membrane, isthmus, and the central group of lymph nodes. The middle thyroid pedicle was ligated and divided using a harmonic shear, and thyroidectomy was performed, confirming the middle and inferior thyroid pedicle, recurrent laryngeal nerve, as well as the superior and inferior parathyroid gland. The unilateral thyroid specimen was removed through the left axillary incision using an endopouch, and the contralateral lobe was dissected in the same manner. Antiadhesive solution was applied on the whole flap after thyroidectomy, and one Jackson-Pratt drain was placed through the left axillary incision. A surgical brassiere was applied to compress the flap after surgery.

Assessment of outcomes

The primary outcome was acute postoperative pain scores. Postoperative pain in each area (neck, axilla, and ant chest) was reported by patients on a 101-point Numerical Rating Scale (NRS), from 0 (no pain) to 100 (the worst pain

imaginable), at 1, 6, 24 and 48 hours after surgery. Secondary outcomes were as follows: The need for postoperative rescue analgesics, recovery profiles, postoperative adverse events, and chronic pain and discomfort at 3 months after the operation. Patients were examined every 15 minutes using the modified Aldrete scoring system, and discharged from PACU when modified Aldrete score reached 9 or more.[13] Intravenously fentanyl 50 μg was used as the first line rescue analgesics and ketorolac tromethamin 30 mg was used as the second-line if NRS was more than 30 at PACU. In the ward, patients received intravenously ketolorac tromethamin 15 mg if NRS was more than 30 or if patients wanted analgesic drugs. Postoperative adverse events, such as PONV, shivering, headache, dizziness, or drowsiness, were recorded as it occurred during the study period. Chronic pain and discomfort were recorded using 101-point NRS, and the incidence of paresthesia and hypesthesia were also tracked for each area (anterior chest, axilla and neck area) at 3 months after surgery.

Sample size

Sample size was calculated based on mean pain scores of 6 (3.5) 1 hour after robot thyroidectomy[8] using G* power 3.0. We considered that a decrease of 2 in the mean pain scores would be clinically significant. Since each group required 26 patients ($\alpha = 0.05$, $\beta = 0.2$), we decided a total of 58 patients would be needed, considering 10% drop-out rate.

Statistical analysis

SPSS 21 (SPSS, Inc., Chicago, IL) was used for statistical analysis. We performed the Shapiro-Wilk test to determine the normal distribution. Student *t* test was used to compare normally distributed variables (tumor size, resected thyroid weight, and PACU discharge time), and the Mann-Whitney *U* test was performed to compare not normally distributed continuous variables. Repeated measures of analysis of variance (ANOVA) were performed to analysis of postoperative pain scores (NRS) over time. Chi-square test or Fisher exact test was used to analyze other categorical outcomes such as the use of rescue analgesics, adverse events and chronic sensory disturbance. A full analysis set was used for the analysis of data. All values presented are mean (SD), median (IQR), or number of patients (%). A *P* value of < 0.05 was considered to indicate a statistically significant difference.

RESULTS

Sixty-three eligible patients were screened between June 2016 and January 2017, and 58 patients were enrolled and included for final analysis (Fig. 1). Clinical characteristics are shown in Table 1. Patients, surgery, and anesthetic characteristics were comparable between the two groups (Table 1). There were 48 females and 10 males, with a mean age of 36 and 40 years, respectively. The surgical procedures were completed successfully in all patients. BABA robotic and endoscopic thyroidectomy was performed in fifty-three and five patients, respectively. No cases were converted to open thyroidectomy. Postoperative pathology of patients revealed 53 patients with papillary carcinoma, 3 with nodular hyperplasia, 1 with hurtle cell adenoma, and 1 with cellular adenomatoid nodule. There were no significant differences in the pathologic type or tumor size between the two groups.

Primary outcome: pain score

There were statistically significant differences in pain scores between the two groups during a postoperative period of 48 hours. Patients in the nefopam group showed lower pain scores in the neck, axilla, and chest areas compared with those in the control group at postoperative 1, 6, 24, and 48 hours (Fig. 2).

Secondary outcome measures

Rescue analgesic requirements

Statistically significant difference was observed with respect to the need for rescue analgesics between the two groups. Patients in the nefopam group required a smaller number of rescue analgesic administrations than in the control group during the postoperative 48 hours (1.4 [1.0] vs 2.3 [1.5]; $P = 0.001$).

Recovery profiles

The length of stay in PACU was similar between the two groups. There were no major adverse events during the study period in the nefopam group. Postoperative complications, including shivering, headache, dizziness, and PONV, were reported during the study period. However, there were significantly less incidences of shivering and headache in the nefopam group than in the control group (1 [3] vs 10 [34]; $P = 0.005$, 8 [28] vs 18 [62]; $P = 0.017$). There were no significant differences in other postoperative complications between the two groups (Table 2).

Chronic pain and discomfort

At 3 months after surgery, patients were asked about chronic pain and discomfort at the anterior chest, axilla and neck areas, and the VNRS in the nefopam group were lower than that in the control group for each area (Table 3). The incidence of chronic sensory disturbance, including paresthesia and hypesthesia, between the two groups did not reach statistical significance (Table 3).

Table 1. Patient, anesthesia, and surgery characteristics

	Control group (n = 29)	Nefopam group (n = 29)	*P* value
Age, yr	36 (9)	40 (9)	0.064
Male/female, %	6 (20) / 23 (80)	4 (14) / 25 (86)	0.730
Weight, kg	64 (14)	61 (9)	0.254
Height, cm	164 (9)	163 (6)	0.657
ASA class, I/II	29 (100) /0 (0)	28 (97) /1 (3)	> 0.999
Robot/endoscopy	26 (90) /3 (10)	27 (93) /2 (7)	
Uni/total/isthmectomy	17(59) /10 (34) / 2 (7)	13 (45) / 15 (52) /1 (3)	0.393
Anesthesia time, min	192 (44)	200 (33)	0.413
Operation time, min	151 (41)	160 (31)	0.333
Amount of drainage, ml	188 (31)	137 (46)	0.658
Benign/malignant	4 (14) / 25 (86)	1 (3) / 28 (97)	0.205
PTC	25	28	
Nodular hyperplasia	3	0	
Others	1	1	
Tumor size, cm	1.4 (0.9)	1.3 (0.9)	0.956
Resected thyroid weight, g	10.5 (6)	10.3 (4.5)	0.584

Values are given as mean (standard deviation), median (IQR) or number of patients (%). ASA class = American society of Anesthesiologist physical class, PTC; papillary thyroid carcinoma, Uni = unilateral thyroidectomy

Table 2. Postoperative recovery profile

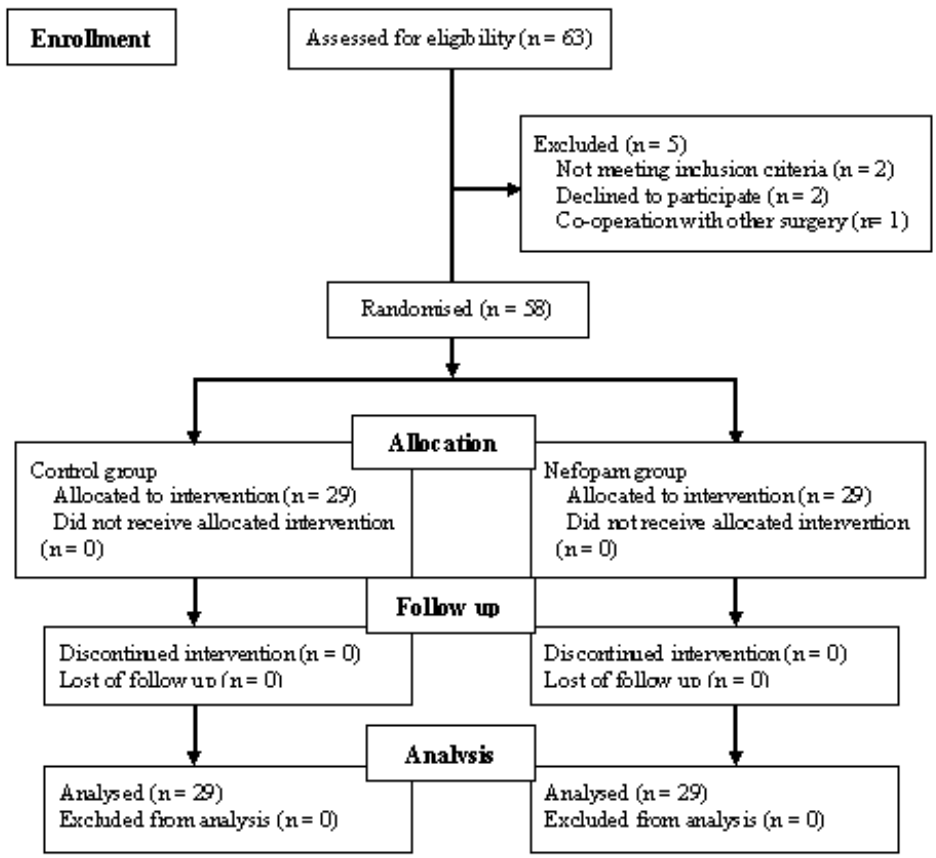
	Control group (n = 29)	Nefopam group (n = 29)	*P* value
Length of stay in PACU, min	35 (9)	36 (7)	0.454
Shivering	10 (34)	1 (3)	0.005
Headache	18 (62)	8 (28)	0.017
Dizziness	7 (24)	3 (10)	0.297
PONV	3 (10)	1 (3)	0.611

Discharge time: the achievement of a modified Aldrete score of 9. All values are given as median (interquartile range) or number (%). PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting.

Table 3. Chronic discomfort and sensory disturbance

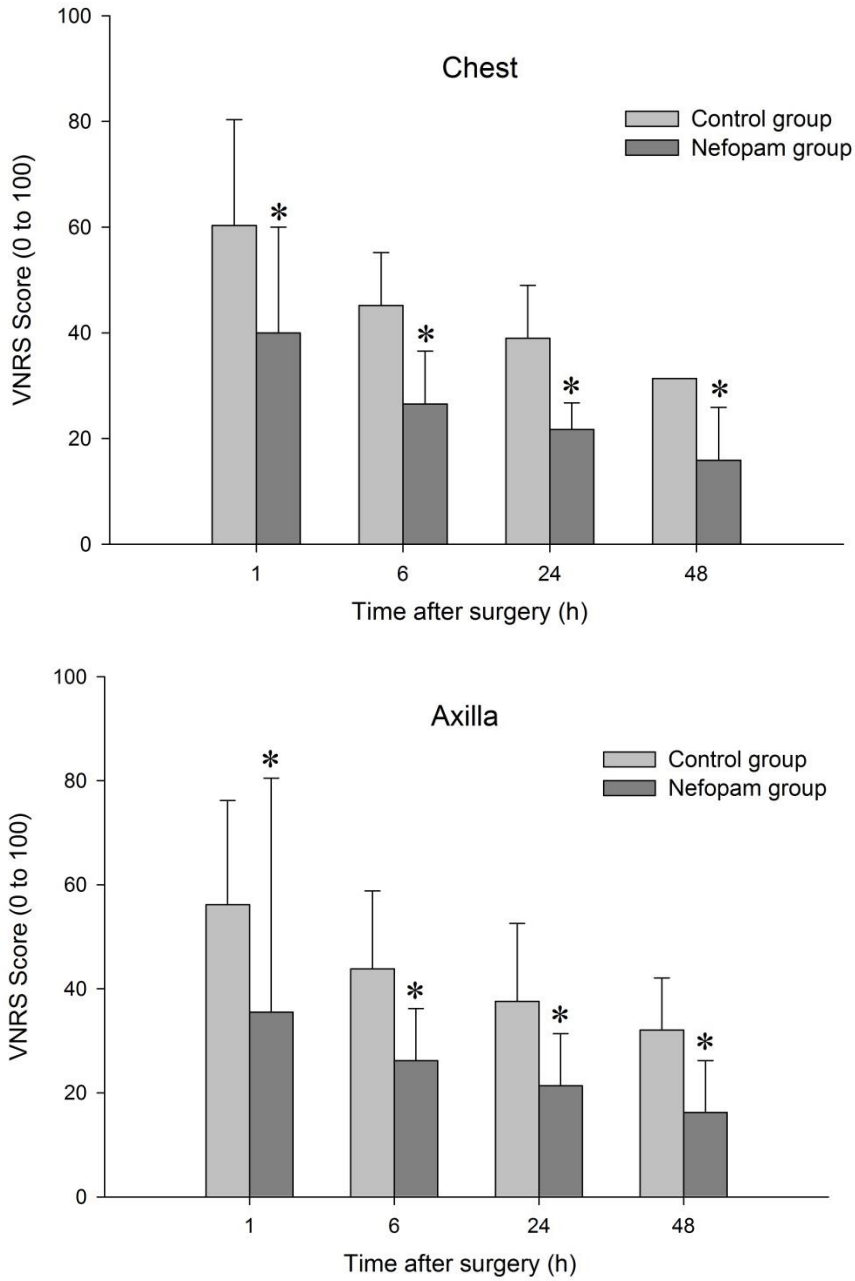
	Control group (n= 29)	Nefopam group (n = 29)	*P* value
Chest			
Pain and discomfort	0 (10)	0 (0)	< 0.001
Sensory disturbance	5	6	> 0.999
Axilla			
Pain and discomfort	0 (10)	0 (0)	0.005
Sensory disturbance	4	2	> 0.999
Neck			
Pain and discomfort	0 (20)	0 (0)	< 0.001
Sensory disturbance	16	9	0.331

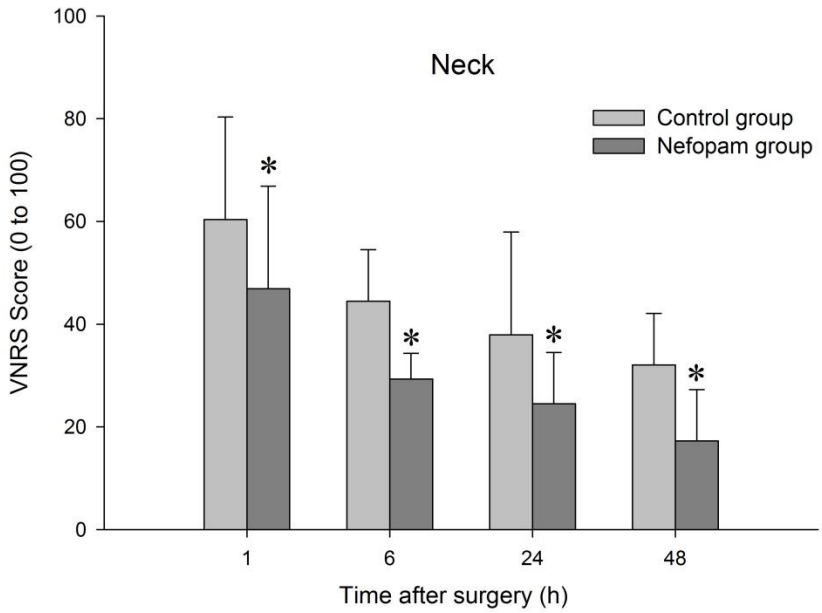
Figure 1. CONSORT diagram for the trial



Sixty three patients were screened for eligibility and 58 patients were randomized.

Figure 2. Acute postoperative pain score of anterior chest, axilla, and neck area using verbal numerical rating scale (VNRS)





Pain score of nefopam group at each area were lower than that of control group at 1, 6, 24, and 48 h postoperatively. *; $P < 0.05$ compared with control group.

DISCUSSION

To the best of our knowledge, this is the first study to assess the analgesic efficacy of nefopam for acute and chronic pain after robotic or endoscopic thyroidectomy. The results of this prospective randomized clinical trial suggest that intraoperative administration of IV nefopam (0.2 mg/kg bolus dose and 120 μg/kg/h continuous infusion) reduced acute postoperative pain and prevented the development of chronic pain and hypoesthesia without adverse events in patients undergoing robotic or endoscopic thyroid surgery via BABA.

For robotic or endoscopic thyroidectomy, BABA was used to achieve a lateral operative view that is comparable to open surgery and to provide excellent postsurgical aesthetic appearance without scars on the anterior neck.[13] This approach uses two breasts and two axillary skin incisions and ports. Additionally, BABA requires a broad dissection of subplatysmal skin flaps, from the axilla to the anterior neck, and a forceful lifting of the tissues during surgery with CO_2 gas insufflation on the neck and anterior chest areas, which likely explains the cause of acute postoperative pain. Postoperative pain after endoscopic thyroidectomy has been known to be localized in the anterior chest, neck and axilla areas, which may be associated with the skin dissection of the subcutaneous tissue and the thermal damage from electric cautery of these areas.[14] In the current study, the pain scores in the nefopam group were lower than those in the control group with respect to the neck, anterior chest and axilla areas. Moreover, rescue analgesics were required less in the nefopam group than in the control group. Nefopam has been used to

manage postoperative pain as one of the multimodal analgesia.[10] The finding of this study suggests that a single infusion of intraoperative nefopam may provide postoperative analgesia, which may be explained by the preemptive analgesic action of nefopam.

In addition to acute postoperative pain, the present study also assessed the effect of intraoperative nefopam infusion on the development of chronic pain and discomfort. Acute postoperative pain has been known to be a predictive factor for the development of long-term sensory disturbances resulting in chronic discomfort, dysesthesia or hypoesthesia.[15] Robotic thyroidectomy has been associated with greater anterior chest discomfort and sensory disturbances than conventional open thyroidectomy. Moreover, it has also been associated with the need for longer recovery periods. These chronic symptoms may persist for as long as 3 months post robotic or endoscopy-assisted thyroidectomy.[15] Intraoperative administration of nefopam reduced chronic pain that were evaluated at postoperative 3 months, although the incidence of chronic sensory disturbances, including paresthesia and hypesthesia between the two groups, did not reach statistical significance. This result may be explained as follows: Nefopam may act as N-methyl-D-aspartate (NMDA) receptor antagonist, reducing wind-up and central sensitization.[11] A previous investigation also reported that preventive nefopam reduced the occurrence of chronic pain, as well as acute pain after breast cancer surgery.[16]

In this current study, postoperative adverse events, including shivering, headache, dizziness, and PONV, were recorded for the study period, and the incidence of

shivering and headache were significantly lower in the nefopam group than in the control group. Shivering is a distressing and frequent complication following surgery and anesthesia. A meta-analysis of nefopam for preventing perioperative shivering concluded that nefopam is associated with decreased risk of postoperative shivering.[17] It has previously been established that by increasing the core temperature and lowering the shivering threshold, nefopam has anti-shivering effect.[18]

There are a few limitations to consider when interpreting our results. First, rescue analgesics were administered as postoperative pain control, instead of patient-controlled analgesia (PCA). Opioid-based PCA has been used as postoperative pain control in patients undergoing robotic or endoscopic thyroidectomy in our institution; but high incidence of PONV following thyroidectomy limited the use of opioid-based PCA.[6] Second, the efficacy profiles of patients in the nefopam group were compared with those in the control group instead of other analgesics since analgesic modality following robotic or endoscopic thyroidectomy has not been established. Several analgesic modalities have been investigated to find effective analgesia after robotic or endoscopic thyroidectomy,[7-9, 12] and further studies are needed to compare these methods in terms of efficacy and safety profiles.

In conclusion, an intraoperative administration of intravenous nefopam has shown to effectively reduce acute postoperative pain and rescue analgesic requirement, as well as chronic pain and discomfort in patients undergoing robotic or endoscopic thyroidectomy via BABA without adverse effects. Further studies are necessary to

establish an effective analgesic modality after robotic or endoscopic thyroidectomy to increase the quality of recovery and better manage postoperative pain.

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국 문 초 록

서론: 로봇 혹은 내시경 갑상선 절제술 후에는 급성 통증과 만성 불편감이 있는 것으로 알려져있다. 이 전향적 무작위배정 이중맹검 연구의 목적은 수술 중 투여한 네포팜이 양측 액와-유방접근법으로 로봇 혹은 내시경 갑상선 절제술을 받은 환자의 수술 후 급성 통증과 만성 불편감을 감소시킬 수 있는지를 알아보는 것이다.

방법: 환자들은 무작위로 두 군으로 배정되었다: 대조군 (29명) 혹은 네포팜 군 (29명). 각 군의 환자들에게 수술 중 동량의 생리식염수 혹은 네포팜 (0.2 mg/kg bolus, 120 μg/kg/h continuous infusion) 을 투약하였다. 수술 후 급성 통증, 추가 진통제 투여 횟수. 기타 다른 부작용들이 수술 1, 6, 24, 그리고 48시간 후에 평가되었다. 만성 통증과 불편감은 수술 3개월 후 기록되었다.

결과: 수술 1, 6, 24, 그리고 48시간 후에 목과 겨드랑이, 그리고 전흉부에서 평가된 네포팜 군 환자들의 통증점수는 대조군 보다 낮았다 ($P < 0.05$). 네포팜 군의 진통제 투여 횟수도 대조군 보다 적었다 (1.4 [1] *vs.* 2.3 [1.5]; $P = 0.001$). 만성 통증과 불편감의 정도도 네포팜 군에서 상대적으로 낮았다 ($P < 0.05$).

결론: 수술 중 네포팜을 정맥내로 투여하는 것은 양측 액와-유방 접근법으로 로봇 혹은 내시경 갑상선 절제술을 받는 환자에서 수술 중 네포팜을 정맥내로 투여하는 것은 부작용 없이 수술 후 급성 통증과 진통제 투여 횟수 및 만성 불편감을 줄일 수 있다.

주요어: 급성 통증, 내시경 갑상선 절제술, 네포팜, 로봇 갑상선 절제술, 만성 불편감.

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