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The effect of nicardipine on the surgical pleth index during thyroidectomy under general anesthesia

A prospective double-blind randomized controlled trial

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Abstract

Background: The effectiveness of surgical pleth index (SPI) for managing nociception-antinociception balance during general anesthesia with vasodilators, including nicardipine has not been demonstrated. We aimed to compare the time course during surgery in SPI values in patients receiving nicardipine or remifentanil infusion during thyroidectomy.

Methods: Forty patients undergoing thyroidectomy were randomly assigned to receive nicardipine (group N; n = 19) or remifentanil (group R; n = 21) along with induction (propofol, fentanyl, and rocuronium) and maintenance (50% desflurane/nitrous oxide in oxygen) anesthesia (goal bispectral index [BIS] ~50). The infusion of nicardipine or remifentanil was started before the 1st incision and adjusted to keep mean blood pressure (MBP) within ±20% of the preoperative value. SPI, BIS, end-tidal desflurane concentration (EtDes), MBP, and heart rate were recorded at 2.5 minute intervals from the 1st incision to the end of surgery. Extubation and recovery times, pain score/rescue ketorolac consumption, and adverse events in postanesthesia care unit (PACU) were recorded.

Results: The trend of SPI during surgery was comparable between the 2 groups ($P = 0.804$), although the heart rates in group N were significantly higher than those in group R ($P = 0.040$). The patient characteristics, trends of BIS, EtDes, and MBP during surgery, extubation and recovery times, and incidence of nausea/vomiting were comparable between the groups. Group N had significantly lower pain scores and rescue ketorolac consumption at PACU.

Conclusion: SPI was comparable between patients receiving nicardipine or remifentanil infusion during thyroidectomy under general anesthesia, which suggests that the administration of nicardipine may confound the interpretation of SPI values during general anesthesia.

Clinical trial registration: This trial was registered in the UMIN clinical trials registry (unique trial number: UMIN000019058; registration number: R000022028; principal investigator's name: Young Ju Won; date of registration: September 17, 2015).

Abbreviations: BIS = bispectral index, BP = blood pressure, EtDes = end-tidal desflurane concentration, HBI = heart beat-to-beat interval, HR = heart rate, IQR = interquartile range, MBP = mean blood pressure, NRS = numerical rating scale, PACU = postanesthesia care unit, PPGA = photoplethysmographic waveform amplitude, SPI = surgical pleth index, TOF = train-of-four.

Keywords: analgesics, calcium channel blocker, nicardipine, opioid, pulse oximetry, remifentanil

1. Introduction

The surgical pleth index (SPI) is a monitoring tool derived from finger photoplethysmographic signals for detecting the balance between nociceptor activation and analgesic administration during general anesthesia.[1] SPI values are calculated by the following equation: $SPI = 100 - (0.33 \times HBI + 0.67 \times PPGA)$; HBI = the heart beat-to-beat interval, PPGA = the photoplethysmographic

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waveform amplitude.[2] An SPI range of 20 to 50 has been used to reflect adequate analgesia in previous studies.[3–6]

The effectiveness of SPI for quantifying nociception during general anesthesia has been demonstrated in many clinical settings.[5,6] However, the clinical application of SPI may have considerable limitations associated with the patient population,[7] positioning,[8] fluid balance,[9] type of anesthesia,[10] or concomitant use of cardiovascular drugs.[11] Concerning the use of cardiovascular drugs during anesthesia, although SPI could differentiate the hemodynamic action of a β-blocking agent (esmolol) from the analgesic action of remifentanil,[11] its effectiveness has not been proven in the clinical setting with the use of vasodilators, such as nicardipine. Nicardipine is a calcium channel blocker that can be infused intravenously. It is easily titrated to achieve rapid blood pressure (BP) control because it has a relatively rapid onset/offset of action similar to remifentanil.[12]

We aimed to compare the time course during surgery in SPI values between patients receiving nicardipine infusion and those receiving remifentanil infusion during thyroidectomy under general anesthesia. We hypothesized that SPI would be higher in patients receiving nicardipine than in those receiving remifentanil while keeping the bispectral index (BIS) around 50, when considering the opposite effects on the heart rate (HR) between the 2 drugs (the increase in HR by nicardipine vs the decrease in HR by remifentanil).

2. Materials and methods

This study was a single-center prospective double-blinded randomized controlled trial performed at Korea University Guro Hospital, Seoul, South Korea, from September 2015 to February 2016. After obtaining approval from the Korea University Guro Hospital Institutional Review Board, the trial was registered in the UMIN clinical trials registry (unique trial number: UMIN000019058; registration number: R000022028; principal investigator's name: Young Ju Won; and date of registration: September 17, 2015). All patients were recruited from the Department of Breast Endocrine Surgery, Korea University Guro Hospital by the research staff. Patients were enrolled in the study at admission to the hospital the day before surgery. After an explanation of the trial, written informed consent was obtained from all participants.

Patients scheduled to undergo elective thyroidectomy, aged 20 to 65 years, and had an American Society of Anesthesiologists physical status I or II with a normal thyroid function, were included in the study. Exclusion criteria included a history of cardiovascular, renal, endocrine, neuromuscular, or neurological diseases, abuse of alcohol or illicit drugs, or taking medication that may affect autonomic regulation (eg, β-blocker, clonidine), and pregnancy.

Patients were randomly allocated to the nicardipine (group N) or the remifentanil (group R) group based on the drug chosen for infusion, and they were unaware of the assigned group. A single investigator was responsible for the group assignment of patients. Randomization was achieved using a web-based computer-generated list (www.randomization.com). The numbers were kept in opaque, sealed envelopes that were opened in the operating room by an independent anesthesiologist not involved in the study.

All patients were premedicated with 7.5 mg of oral midazolam 30 minutes before anesthesia induction. After arriving to the operating room, noninvasive BP, electrocardiogram, pulse oximetry (CARESCAPE monitor B650, GE healthcare), and BIS (BIS-Vista, Aspect Medical Systems, Newton, MA) were monitored in all patients. In all patients, the SPI sensor was attached to the index finger of the arm without the BP cuff. The baseline values for mean blood pressure (MBP), HR, SPI, and BIS were recorded before anesthesia induction.

A single investigator who was responsible for the group assignments prepared the bolus and infused solution of the study drug. For preparation of the bolus of the study drug, either nicardipine (100 μg) or remifentanil (50 μg) was diluted in 0.9% isotonic saline to a final volume of 5 mL (final concentrations: nicardipine 20 μg/mL; remifentanil 10 μg/mL) in a 5-mL polyethylene syringe (KOVAX-SYRINGE; Korean Vaccine, Seoul, Korea), which was labeled as "Bolus X." For preparation of the infused solution of the study drug, either nicardipine (10 mg) or remifentanil (1 mg) was diluted in 0.9% isotonic saline to a final volume of 50 mL (final concentrations: nicardipine 200 μg/mL and remifentanil 20 μg/mL). The solution was then drawn into a 50-mL polyethylene syringe (KOVAX-SYRINGE; Korean Vaccine, Seoul, Korea) and placed on an infusion pump (INJECTOMAT MC AGILIA; Fresenius Kabi, Bad Homburg, Germany). The infusion pump was labeled as "Infusion X." The infusion rate was set using a unit of microgram (dose) per kilogram (body weight) per minute (time).

All anesthetic procedures were carried out by 2 independent anesthesiologists not involved in the study. A blinded independent anesthesiologist performed the induction and maintenance of anesthesia, administered the study drug according to the study protocol, and recorded the values. The other blinded independent anesthesiologist assessed the extubation time and postoperative pain during the emergence and recovery phases.

Anesthesia induction was achieved with propofol 2 mg/kg, fentanyl 1 μg/kg, rocuronium 0.6 mg/kg, and mask ventilation with desflurane 5 vol% and oxygen 8 L/minute for 2 minute 30 seconds, followed by intubation. Mechanical ventilation was maintained at a tidal volume of 8 mL/kg, and ventilation frequency was adjusted to maintain an end-tidal carbon dioxide between 30 and 35 mm Hg. Anesthesia was maintained and continuously adjusted with desflurane 4 to 6 vol% in 50% nitrous oxide–oxygen, both at 1.5 L/minutes to achieve a BIS of approximately 50.

Before the 1st incision, the patients in group N were administered the 100 μg nicardipine bolus ("Bolus X") and the infusion of nicardipine at 0.5 μg/kg/minute ("Infusion X"). The infusion was maintained at that rate until the skin incision, after which it was titrated by increasing or decreasing 0.1 μg/kg/minute step wisely at intervals of 2.5 minutes to keep MBP within ±20% from baseline during surgery. For the patients in group R, the 50 μg remifentanil bolus ("Bolus X") was administered, followed by the 0.05 μg/kg/minute infusion ("Infusion X"), which was maintained until the skin incision and titrated using the same method by increments or decrements of 0.01 μg/kg/minute.

SPI, BIS, end-tidal desflurane concentration (EtDes), MBP, and HR were recorded at 2.5-minute intervals from the 1st incision until the end of surgery. For the proper neuromuscular blockade, neuromuscular function was monitored with acceleromyography, using the train-of-four (TOF)-Watch SX (Organon Ireland Ltd, Schering-Plough Corporation, Dublin, Ireland). Rocuronium (5 mg) was additionally administered at the reappearance of a TOF count of 2 just until the removal of the thyroid gland.

At the point of the skin suture, propacetamol hydrochloride (1 g mixed in 100 mL of 0.9% normal saline) was administered intravenously for postoperative pain control. At the end of surgery, the administration of desflurane and nitrous oxide was stopped, and fresh gas flow was increased to 8 L/minute of

oxygen, and pyridostigmine 10 mg and glycopyrrolate 0.4 mg were administered for the reversal of neuromuscular blockade, after confirming a TOF count of 4.

After the patient recovered spontaneous breathing and consciousness, extubation was performed and the patient was transferred to the postanesthesia care unit (PACU). Extubation time was considered as the time from the discontinuation of anesthetics to extubation and assessed by the blinded independent anesthesiologist.

In the PACU, the blinded independent anesthesiologist assessed the recovery time (time to reach a modified Aldrete score of 10), numerical rating scale (NRS; 1–10) for pain every 10 minutes for 60 minutes, cumulative consumption of rescue ketorolac, and the occurrence of adverse events.

For postoperative pain control, ketorolac 15 mg was administered for an NRS score over 4 and the treatment was repeated at 10-minute intervals. Metoclopramide hydrochloride hydrate (10 mg) was administrated for nausea or vomiting. The cumulative consumption of rescue ketorolac and incidences of adverse events, including nausea or vomiting, were recorded.

The primary endpoint of this study was to compare the time course during surgery in SPI values between the patients receiving nicardipine and those receiving remifentanil during thyroidectomy under desflurane anesthesia. Secondary endpoints were extubation and recovery times, trends of intraoperative BIS, EtDes, MBP, HR, and NRS for pain, cumulative rescue ketorolac consumption, and incidences of adverse events in the PACU.

2.1. Statistical analysis

Since SPI was the prior endpoint in this study, the sample size was calculated based on the results of the SPI values (mean [standard deviation] = 59 [3.6] in patients receiving esmolol; 55 [5.0] in patients receiving remifentanil at 2–12 minutes after the trocar insertion during surgery) in a previous report by Ahonen et al,[11] using G*Power software, version 3.1 (Franz Faul, Universität Kiel, Kiel, Germany). Therefore, the effect size of 2 groups was 0.91. On the assumption the allocation ratio of 2 groups was 1, a sample size of 20 patients was selected for each group, calculated by Student and 2-sided *t* tests with a level of significance of 0.05 and a power of 0.8. We estimated a 10% dropout, resulting in the final enrolment of 22 patients in each group (total = 44 patients).

Statistical analysis was performed with SPSS software, version 18 (SPSS Inc., IBM, Chicago, IL). Trends of SPI, BIS, EtDes, MBP, and HR during surgery between the 2 groups were compared by repeated measures analysis of variance factoring for time and group assignment (type III sum of squares). Continuous data (age, body mass index, anesthesia and surgical times, intraoperative fluid amount, baseline values of SPI, MBP and HR, extubation time, recovery time, NRS for pain, and rescue ketorolac consumption in the PACU) between the groups were analyzed using a 2-tailed Student *t* test (normally distributed data) or Mann–Whitney *U* test (abnormally distributed data). Categorical data (sex and the incidence of nausea or vomiting in the PACU) between the groups were compared using a Chi-squared test. The data are expressed mean, median (25th–75th percentiles [interquartile range]), or number of patients (%). A *P*-value <0.05 was considered statistically significant.

3. Results

Briefly, a total of 48 patients were assessed for eligibility, 44 of them were enrolled in the study, and 40 completed the study. Nineteen patients were included in group N and 21 in group R (Fig. 1).

There was no significant difference between the 2 groups in age, sex, body mass index, and clinical data, which includes anesthesia and surgical times, intraoperative fluid amount, and the baseline values of SPI, MBP, and HR (Table 1).

The trend of SPI was comparable between the groups during surgery ($P = 0.804$); however, the trend of the HR was significantly higher in group N than in group R ($P = 0.040$) (Fig. 2).

Intraoperative BIS, EtDes, and MBP were comparable between the 2 groups (Fig. 3). The following intraoperative hemodynamic events occurred: 3 events of bradycardia (HR < 50 beats per minute) in group R, but all events spontaneously resolved after lowering the infusion rate of remifentanil; no bradycardia in group N; and no events of hypotension or hypertension (MBP <80% or >120% of the baseline value, respectively) that lasted for over 2.5 minutes in either group.

Extubation time was comparable between the 2 groups (Table 2).

In the PACU, recovery time was comparable between groups N and R (Table 2). NRS scores for pain were significantly lower in group N than in group R at 30 minutes (4 [4–4] vs 6 [4–7], $P = 0.003$), 40 minutes (3 [3–4] vs 4 [4–6], $P = 0.005$), and 50 minutes (3 [3–4] vs 4 [3–4.5], $P = 0.034$) after PACU admission (Fig. 4). Cumulative rescue ketorolac consumption was also significantly lower in group N than in group R (17.4 [16.0] vs 34.3 [17.8] mg, $P = 0.003$) (Table 2).

The incidence of nausea or vomiting in PACU was comparable between the 2 groups (4 [group N] vs 3 [group R] patients, $P = 0.570$). There were no other problematic adverse events, such as hypotension, desaturation, or laryngospasms in the PACU.

4. Discussion

It has been shown that the SPI correlates with both the intensity of surgical stimuli and the effect of antinociceptive drug during general anesthesia.[2,5,13–17]

However, SPI values may also be affected by other factors, including the type of anesthesia,[10] age[18] or positioning of the

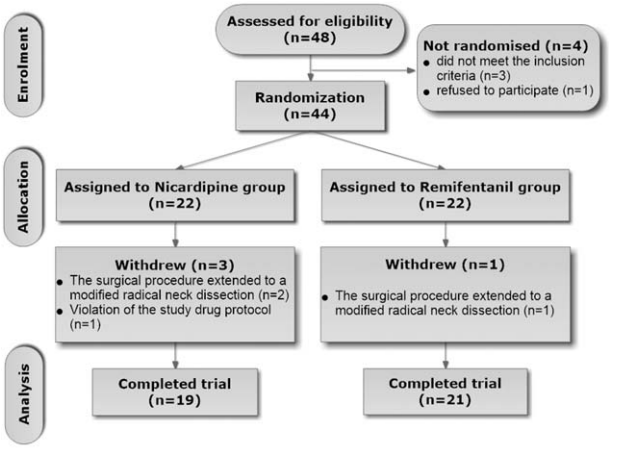

Figure 1. A flow chart describing patient recruitment, randomization, and withdrawal. Initially, 44 patients were randomly assigned to 1 of 2 groups as follows: the nicardipine infusion group (group N) or the remifentanil infusion group (group R). Forty patients (19 in group N and 21 in group R) completed this study.

Table 1

Demographic and clinical data. .

	Group N (n=19)	Group R (n=21)
Age, year	46 [26–60]	46 [34–68]
Sex (M/F)	3/16	4/17
Body mass index, kg/m^2	24.5 (2.6)	23.6 (2.5)
Anesthesia time, minute	97.4 (26.0)	101.9 (20.4)
Surgical time, minute	69.6 (23.8)	70.5 (18.2)
Intraoperative fluid amount, mL/kg	4.1 (2.5)	3.7 (1.5)
Baseline SPI value	45.2 (19.1)	49.4 (18.9)
Baseline mean arterial pressure, mm Hg	92.7 (10.6)	93.3 (7.8)
Baseline heart rate, beats/minute	71.0 (13.6)	75.4 (16.4)

Values are represented as mean (SD), median (range), and number of patients. Group N, nicardipine infusion group. Group R, remifentanil infusion group. No statistically significant differences were observed between the 2 groups. Baseline: before induction of anesthesia. SD = standard deviation, SPI = surgical pleth index.

patient,[8] fingertip temperature, intravascular volume status,[9] prescribed hypertensive drugs,[1] and the concomitant use of cardiovascular drugs such as esmolol or labetalol during surgery.[6,11] In terms of the use of cardiovascular drugs during anesthesia, it is very difficult for us to predict the final results of SPI values since their effect on the SPI is complex.

The results of the present study demonstrated that SPI values were not different between patients receiving a nicardipine or remifentanil infusion during thyroidectomy under general anesthesia, even though the HRs were higher in the nicardipine group. Based on the assumption that vasodilators typically elevate the HR, which would make HBI shorter and the SPI values higher, but opioids including remifentanil usually decrease the HR, we hypothesized before performing this study, that SPI would be higher in patients receiving nicardipine than in those receiving remifentanil. However, vasodilators might increase the PPGA, due to the increase of the peripheral perfusion, followed by vasodilation of peripheral arterioles, which might result in decreased SPI values.[19] Therefore, considering the counteracting effects of nicardipine on the HBI and PPGA, the 2 main variables determining the SPI, the final results of the SPI values in the nicardipine group might be quite unpredictable. Nevertheless, we finally speculated that in this study, the lowering effect of nicardipine on the SPI level would be inferior to that of remifentanil, considering that remifentanil could also increase the PPGA by causing a suppression of the sympathetic response.[11] Considering the previously mentioned factors that affect SPI values, we standardized the study population and environment by standardizing the patient characteristics, surgery and anesthesia, and anesthetic management (Table 1), as well as using a standardized study protocol for our double-blind randomized controlled trial.

Consequently, the trend of SPI values was unexpectedly comparable between the 2 groups, although HR was higher in the nicardipine group. With regards to the differential action on vascular versus cardiac muscle, nicardipine has been known to have at least twice as much vascular selectivity than other calcium channel antagonists (verapamil, diltiazem, and nifedipine).[20] Considering that the BIS scores of the 2 groups were similar under anesthesia with desflurane combined with nitrous oxide, the

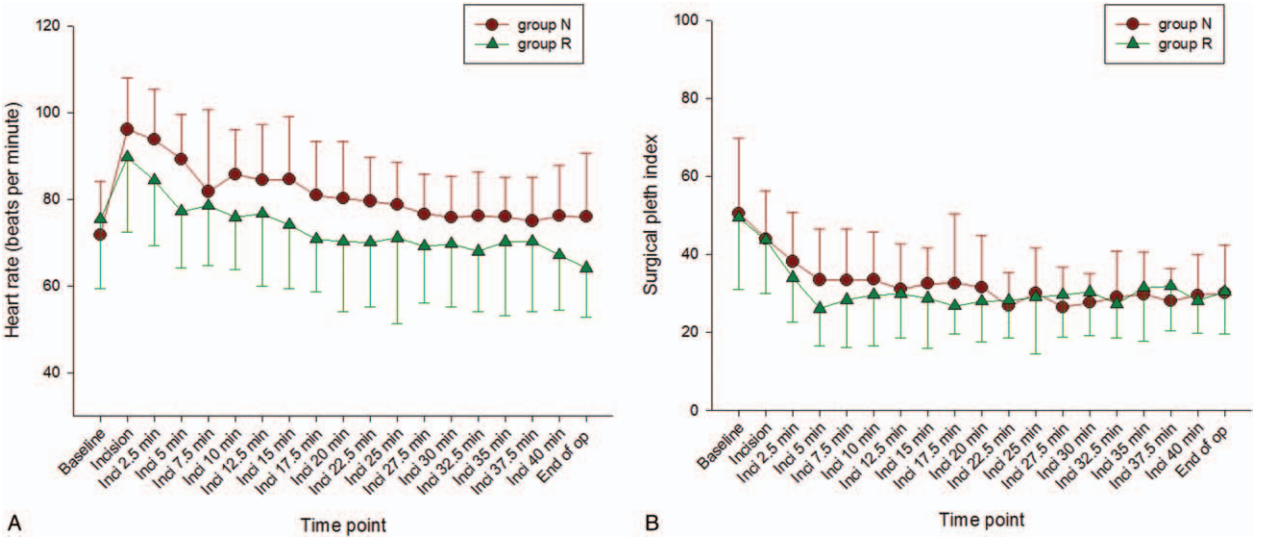

Figure 2. Trends of heart rate (left) and surgical pleth index (right) in patients receiving nicardipine (group N) or remifentanil (group R) during surgery. The graphs show the mean value and standard deviation of each variable for each time point during general anesthesia. All data were collected at baseline, incision, 2.5 to 40 minutes after incision, and at the end of the surgery. Repeated measures analysis of variance factoring for time and group assignment (type III sum of squares) showed that the trend of surgical pleth index values was comparable between the 2 groups during surgery ($P=0.804$), but the heart rate was significantly higher in group N than group R ($P=0.040$).

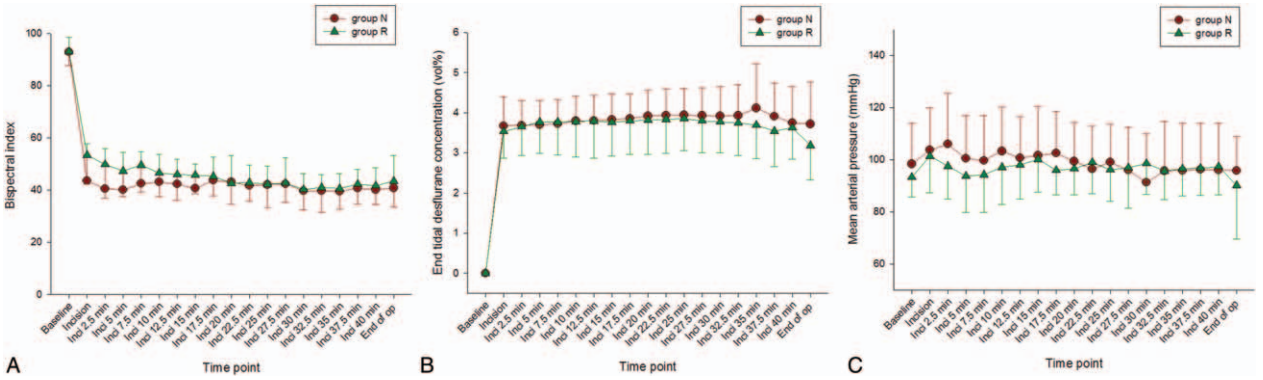

Figure 3. Trends of the bispectral index, end-tidal desflurane concentration, and mean blood pressure in patients receiving nicardipine (group N) or remifentanil (group R) during surgery. The graphs show the mean value and standard deviation of each variable for each time point during general anesthesia. All data were collected at baseline, incision, 2.5 to 40 minutes after incision, and at the end of the surgery. Repeated measures analysis of variance factoring for time and group assignment (type III sum of squares) showed that the trends of the bispectral index, end-tidal desflurane concentration, and mean blood pressure values were comparable between the 2 groups during surgery ($P=0.306$, 0.826, and 0.492, respectively).

elevated HR in the nicardipine group seems to be due to the vasodilatory action of nicardipine and not insufficient anesthesia. In addition, the vasodilatory action of nicardipine can cause an increase of PPGA by increasing peripheral blood flow. PPGA depends on vascular wall distensibility and intravascular pulse pressure, which means that PPGA is highly correlated with the status of peripheral perfusion; thus, PPGA rises proportionately with a rise in peripheral blood flow.[21] Considering that an increased HR causes an increase in the SPI (due to a decreased HBI), but increased PPGA causes a decrease in the SPI, the main result of this study suggests that increased PPGA by nicardipine could be a crucial factor in the SPI values being as low as those of group R. As we can see from the equation for the SPI value, it is determined by 2 factors, HBI and PPGA. HBI contributes to 33% of SPI and PPGA contributes to 66% of SPI. Therefore, it could be that the effect of PPGA on the SPI outweighs and offsets the effect of HBI. Therefore, we suggest that nicardipine may lower SPI values to levels similar to those in the remifentanil group by increasing PPGA despite the increase of HR and decrease of HBI, which may contribute to a misinterpretation of the analgesic state of the patient.

In this regard, we can interpret the results of a previous report by Ahonen et al[11] as follows: unlike nicardipine, esmolol mainly has the effect on lowering HR, with no vasodilatory action. Thus, PPGA can greatly increase in the presence of painful stimuli when there is increased systemic vascular resistance due to a pneumoperitoneum. This can make SPI values higher in patients treated with esmolol than those treated with remifentanil, while maintaining a stable HR and MBP.

In this study, the NRS scores for pain and the consumption of rescue ketorolac in the PACU were significantly higher in patients receiving remifentanil infusion. This may be associated with opioid hyperalgesia or acute opioid tolerance, but the infused dose of remifentanil was relatively low (0.053 ± 0.011 μg/kg/minute). Previous studies have shown that there was no difference in the degree of postoperative pain between the groups of patients given opioids (remifentanil, sufentanil, or oxycodone) according to the criteria of SPI-guided analgesia and those given conventional analgesia based on the hemodynamic monitoring parameters (MBP or HR).[5,6,22] Unlike these studies, remifentanil was only administered in group R during surgery in the present study. In addition, low-dose remifentanil administered during surgery may cause opioid hyperalgesia or acute opioid tolerance, which makes postoperative pain aggravating.[23,24] Therefore, there is the possibility of remifentanil-induced hyperalgesia in this study. More interestingly, there is another issue that is associated with a synergistic analgesic effect of calcium channel blockers with opioids. Early animal studies reported that intrathecal calcium channel blockers had no analgesic effect, but they synergistically potentiated the analgesic effects of opioids.[25] Therefore, in this study, the fact that all patients were given 1 μg/kg of fentanyl at anesthesia induction might explain the lower NRS scores for pain and consumption of rescue ketorolac in the nicardipine group in the PACU. In the same context, this result of our study also corresponds to that of a previous clinical study performed in patients undergoing gynecologic laparoscopy.[26] White et al[26] reported that the intraoperative use of esmolol and nicardipine infusion as an

Table 2

Extubation time, recovery time, PONV incidence, and perioperative medicine.

	Group N (n=19)	Group R (n=21)	Mean difference (95% CI)	P
Extubation time, second	419.8 (105.0)	416.5 (161.6)	3.37 (−84.90–91.63)	0.94
Recovery time, minute	23.7 (9.0)	26.2 (10.7)	−2.5 (−8.86–3.85)	0.43
$Nicardipine_{time}$, μg/kg/minute	0.567 (0.094)			
$Remifentanil_{time}$, μg/kg/minute		0.053 (0.011)		
Nausea or vomiting in PACU	4 (21%)	3 (14%)		0.57
Rescue ketorolac consumption, mg	17.4 (16.0)	34.3 (17.8)	−16.92 (−27.81–6.02)	0.003

Values are mean (SD) or the number of patients (%). Group N, nicardipine infusion group; group R, remifentanil infusion group; extubation time, time from stopping the anesthetic agent to extubation; $nicardipine_{time}$, the infused dose of nicardipine in proportion to time; recovery time, the time to reach a modified Aldrete score of 10 from entering the PACU; $remifentanil_{time}$, the infused dose of remifentanil in proportion to time. CI = confidence interval, PACU = postanesthesia care unit, PONV = postoperative nausea or vomiting, SD = standard deviation.

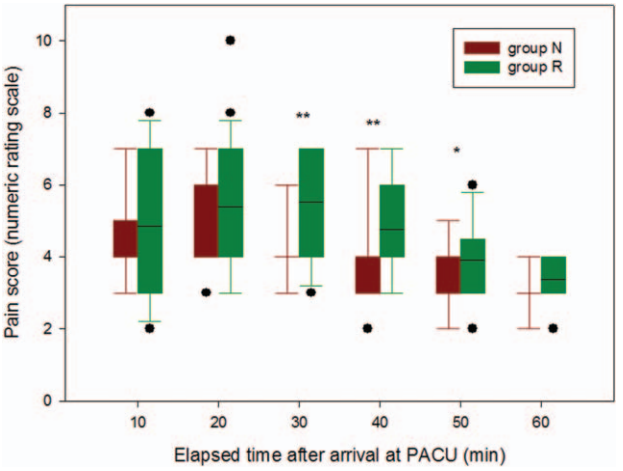

Figure 4. Changes of NRS scores for pain at PACU in patients receiving nicardipine (group N) or remifentanil (group R) during surgery. The graph shows a median and IQR of an NRS score for each time point. The NRS score (median [25th–75th percentiles, IQR]) was lower in group N than in group R at 30 minutes (4 [4–4] vs 6 [4–7], $P=0.003$), 40 minutes (3 [3–4] vs 4 [4–6], $P=0.005$), and 50 minutes (3 [3–4] vs 4 [3–4.5], $P=0.034$) after PACU admission. $*P<0.05$, $**P<0.01$. IQR = interquartile range, NRS = numerical rating scale, PACU = postanesthesia care unit.

adjuvant to desflurane and nitrous oxide during laparoscopic surgery decreased postoperative opioid analgesic requirements. Nevertheless, since it may complicate the main conclusion, we think that further discussion for these issues should be delayed until results from a related study are available.

A limitation in this study was the dosage of infused nicardipine. As the infused dose of nicardipine was low (0.567 ± 0.094 μg/kg/minute) during surgery in this study, we should consider that a higher dose of nicardipine may cause a different change in SPI values under different clinical settings.[27] In this study, the dose of nicardipine was titrated to keep MBP stable and avoid possible hypotension and subsequent organ hypoperfusion[28] during thyroidectomy with relatively low pain. Consequently, the administered dose of nicardipine was low.

In conclusion, there was no difference in the SPI values between the patients receiving nicardipine and those receiving remifentanil during thyroidectomy under general anesthesia. Our data suggest that a nicardipine-induced increase in PPGA could be the crucial factor that lowered the SPI values. SPI does not seem to reflect the level of surgical stress and may not help guide the use of opioids in a clinical setting when nicardipine is administered during general anesthesia. The administration of a calcium channel blocking vasodilator, such as nicardipine, may confound the interpretation of the SPI when used as a surrogate measure of the nociception-antinociception balance.

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