CLINICAL STUDY PROTOCOL & STATISTICAL ANALYSIS PLAN

Comparison of Perioperative Analgesia Nociception Index (ANI) Between Preoperative and Postoperative Ultrasound-Guided Transversus Abdominis Plane (TAP) Block in Laparoscopic Cholecystectomy

Official Study Title	Comparison of Perioperative Analgesia Nociception Index (ANI) between preoperative and postoperative ultrasound-guided Transversus Abdominis Plane Block (TAP block) in laparoscopic cholecystectomy
NCT Number	**NCT ID not yet assigned**
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Principal Investigator	Hyun-Soo Park
Institution	Department of Anesthesiology and Pain Medicine, Pusan National University Yangsan Hospital

1. Protocol Summary

Study Design	Single-center, prospective, single-blind, randomized controlled trial
Study Duration	From Institutional Review Board (IRB) approval through June 30, 2027
Principal Investigator	Hyun-Soo Park, M.D. (Department of Anesthesiology and Pain Medicine, Pusan National University Yangsan Hospital)

2. Background and Scientific Rationale

Although laparoscopic cholecystectomy is generally recognized as a minimally invasive surgical procedure that produces less postoperative pain and facilitates earlier functional rehabilitation than open laparotomy, surgical port incisions and peritoneal insufflation (pneumoperitoneum) inevitably provoke significant visceral and somatic nociception. This post-surgical discomfort remains one of the primary deterrents to uneventful recovery.

As a core component of opioid-sparing multimodal analgesia, ultrasound-guided transversus abdominis plane (US-TAP) block is widely practiced. Administering local anesthetics into the transversus abdominis neurofascial plane blocks cutaneous and muscular nerve branches of the anterior abdominal wall, effectively attenuating incisional and somatic wound pain. Historically, clinical assessment of regional blocks has relied on subjective patient-reported metrics, such as the Visual Analogue Scale (VAS) or Numeric Rating Scale (NRS).

Recently, the Analgesia Nociception Index (ANI)—derived from heart rate variability (HRV) analysis reflecting parasympathetic tone—has been introduced as an objective monitoring parameter rated on a scale of 0 to 100. This clinical trial aims to assess the impact of procedural timing (preoperative vs. postoperative) of US-TAP block on perioperative ANI metrics and clinical analgesic efficacy in patients undergoing laparoscopic cholecystectomy.

3. Study Objectives

Primary Objective: To evaluate and compare intraoperative ANI values—specifically instantaneous (ANI_i) and mean (ANI_m) metrics at major noxious stimuli (skin incision and pneumoperitoneum)—between patients receiving US-TAP block immediately prior to surgical incision versus immediately following fascial closure.

Secondary Objective: To assess postoperative pain scores (VAS) and complication rates up to 24 hours postoperatively, determining whether procedural timing and intraoperative ANI dynamics correlate with recovery quality and postoperative pain intensity.

4. Patient Eligibility Criteria

4.1 Inclusion Criteria

- Patients aged 19 years or older scheduled for elective laparoscopic cholecystectomy.
- American Society of Anesthesiologists (ASA) Physical Status classification I, II, or III.
- Voluntary written informed consent provided prior to participation.

4.2 Exclusion Criteria

- Cognitive impairment or inability to comprehend the protocol and complete pain scales.
- Documented coagulopathy or bleeding diathesis.
- Cardiac arrhythmias or presence of an artificial cardiac pacemaker.
- Concomitant intake of medications altering autonomic tone, including beta-adrenergic blockers and chronic opioids.
- Presence of infection, skin lesions, anatomical scars, or neuromuscular deficits at prospective puncture sites.
- History of allergic reactions or hypersensitivity to ropivacaine.
- Pregnancy or active lactation.

4.3 Withdrawal and Discontinuation Criteria

- **Safety Criteria:** Recurrent serious adverse events (SAEs) causally linked to trial procedures, or symptoms suggestive of Local Anesthetic Systemic Toxicity (LAST).
- **Subject-Related Criteria:** Withdrawal of consent; intraoperative conversion to open laparotomy; unstandardized rescue interventions; or unanticipated severe complications requiring intensive care admission.

5. Sample Size Determination

Based on preliminary data from Kumagai et al. (2025) [1], the median intraoperative ANI changed from 48.0 [42.3–66.5] to 61.0 [50.0–76.5] ($P < 0.01$; standard deviation approximately 17) following peripheral nerve blockade. Assuming a clinically significant difference in ANI of 10 points yields an estimated effect size (Cohen's d) of 0.59.

With a significance level (α) of 0.05 and statistical power ($1 - \beta$) of 80% for an independent two-tailed t-test (G*Power v3.1.9.7), 46 patients per group are required. Adjusting for non-parametric evaluation increases the target to 53 patients per arm. Accounting for an estimated 10% dropout rate, **60 patients per group (total N = 120)** will be enrolled.

6. Study Design and Randomization

This study is designed as a prospective, randomized, single-blind, controlled clinical trial. Participants will be randomized in a 1:1 allocation ratio using a computer-generated random number table (Microsoft Excel, Microsoft Corp., Redmond, WA, USA):

- **Group A (Preoperative Intervention, n = 60):** Receives US-TAP block immediately after general anesthesia induction and prior to surgical skin incision.
- **Group B (Postoperative Control, n = 60):** Receives US-TAP block immediately following surgical port-site closure beneath sterile drapes, prior to emergence.

Participants remain strictly masked to group allocation throughout the trial period.

7. Anesthesia and Interventional Protocol

7.1 Standardized Anesthetic Management

- **Induction:** Propofol (0.6–1.0 mg/kg IV) and rocuronium (0.6–0.8 mg/kg IV) followed by endotracheal intubation.
- **Maintenance:** Sevoflurane (0.8–1.2 MAC) titrated to target a Bispectral Index (BIS) between 40 and 65. Mechanical ventilation adjusted to maintain $EtCO_2$ within 35–45 mmHg. Remifentanil administered via target-controlled infusion (TCI) at a steady effect-site concentration (C_e) of 1.0–1.5 ng/mL.
- **Hemodynamic Stability:** Intravenous ephedrine (5 mg) administered if systolic BP < 70 mmHg or MAP < 65 mmHg. Atropine (0.5 mg) administered for bradycardia (heart rate < 45 bpm). Standard monitoring and ANI sensors are affixed prior to induction.

7.2 Ultrasound-Guided TAP Block Procedure

All regional procedures will be performed under aseptic conditions by an experienced anesthesiologist using a high-frequency linear transducer:

1. **Lateral TAP Block:** 10 mL of 0.2% ropivacaine injected into the transversus abdominis fascial plane at the right flank.
2. **Subcostal TAP Block:** 10 mL of 0.2% ropivacaine injected into the right subcostal transversus plane.
3. **Bilateral Rectus Sheath Block:** 5 mL of 0.2% ropivacaine injected bilaterally into the posterior rectus sheath periumbilically (total volume: 30 mL of 0.2% ropivacaine).

7.3 Postoperative Analgesia and Monitoring

All subjects receive intravenous patient-controlled analgesia (IV-PCA): fentanyl 1000 μg, nefopam 100 mg, and ramosetron 0.6 mg in normal saline (total volume: 100 mL; basal rate: 1 mL/h, bolus: 1 mL, lockout interval: 15 minutes). For breakthrough pain (VAS ≥ 6), step-wise IV rescue analgesics (ketorolac 30 mg, nefopam 20 mg, fentanyl 50 μg, or paracetamol 1000 mg/ibuprofen 300 mg) are administered and recorded.

8. Endpoints and Observational Parameters

Domain	Parameters Recorded	Assessment Timepoints
Primary Endpoints	Instantaneous ANI (ANI_i), Mean ANI (ANI_m), intraoperative duration of ANI < 50 (%)	Baseline (T_0), 1 & 4 min post-incision (T_1), 1 & 4 min post-pneumoperitoneum (T_2), overall surgical duration
Secondary Endpoints	Visual Analogue Scale (VAS 0–10) Cumulative rescue analgesic consumption	PACU arrival, PACU discharge, 12 h, and 24 h postoperatively
Safety & Satisfaction	Complications (PONV, dizziness, LAST symptoms) 5-point Likert patient satisfaction scale	Evaluated continuously up to 24 h postoperatively

9. Statistical Analysis Plan (SAP)

Statistical analyses will be performed using IBM SPSS Statistics for Windows (Version 27.0, IBM Corp., Armonk, NY, USA). Continuous variables will be evaluated for normality using the Shapiro–Wilk test. Normally distributed data will be reported as mean ± standard deviation (SD) and compared using independent-samples t-tests. Non-normally distributed data, including ANI values, will be summarized as median [interquartile range] and analyzed via the Wilcoxon signed-rank test or Mann–Whitney U test. Categorical variables will be expressed as counts and percentages (n, %) and compared using the Chi-square (χ^2) test or Fisher's exact test. A two-tailed $P < 0.05$ is defined as statistically significant.

10. Data Confidentiality and Ethics

This protocol adheres to the Declaration of Helsinki (2013) and ICH-GCP standards, and has received approval from the Institutional Review Board of Pusan National University Yangsan Hospital. All participant data are strictly anonymized with unique subject identification codes. No personally identifiable protected health information is disclosed in public clinical registries or scientific manuscripts.

11. References

1. Kumagai M, Yamada N, Wakimoto M, Ogawa S, Watanabe S, Sato K, Suzuki KS. Effect of postoperative peripheral nerve blocks on the analgesia nociception index under propofol anesthesia: an observational study. *J Clin Monit Comput*. 2025;39(5):967–973.
2. Byeon GJ, Shin SW, Yoon JU, Kim EJ, Baek SH, Ri HS. Infusion Methods for Continuous Interscalene Brachial Plexus

Block for Postoperative Pain Control after Arthroscopic Rotator Cuff Repair. *Korean J Pain*. 2015;28(3):210–216.

3. Trifa M, Ben Khalifa S, Jendoubi A, Zribi N, Regaya T, Engelhardt T. Clonidine does not improve quality of ropivacaine axillary brachial plexus block in children. *Paediatr Anaesth*. 2012;22(5):425–429.
4. Jeanne M, Logier R, De Jonckheere J, Tavernier B. Validation of a graphic measurement of heart rate variability to assess analgesia/nociception balance during general anesthesia. *Annu Int Conf IEEE Eng Med Biol Soc*. 2009;2009:1840–1843.
5. Szental JA, Webb A, Weeraratne C, Campbell A, Sivakumar H, Leong S. Postoperative pain after laparoscopic cholecystectomy is not reduced by intraoperative analgesia guided by analgesia nociception index (ANI®) monitoring: a randomized clinical trial. *Br J Anaesth*. 2015;114(4):640–645.

PART II: SUBJECT INFORMATION SHEET AND INFORMED CONSENT FORM

1. Study Title

Comparison of Perioperative Analgesia Nociception Index (ANI) between preoperative and postoperative ultrasound-guided Transversus Abdominis Plane Block (TAP block) in laparoscopic cholecystectomy)

2. Invitation to Participate

You are being invited to participate in a clinical research study. The Principal Investigator adheres strictly to applicable statutory regulations and ethical principles rooted in the Declaration of Helsinki when obtaining and documenting your voluntary informed consent. Before deciding whether to participate, please read this document carefully. Participation is entirely voluntary. It is essential that you understand why this study is being conducted, how your data will be utilized, what procedures are involved, and the potential benefits, risks, and inconveniences. You may take ample time to deliberate and discuss this trial with your family, friends, or attending physician. If you decide to take part, you will be asked to sign the consent form, and a signed duplicate copy will be provided for your personal records.

3. Purpose of the Study

Ultrasound-guided transversus abdominis plane (US-TAP) block is a regional anesthetic procedure that blocks anterior abdominal sensory nerves by infiltrating local anesthetics into the neurofascial plane between the internal oblique and transversus abdominis muscles. It is widely utilized in clinical practice to alleviate incisional and abdominal wall wound pain following laparoscopic surgery.

The purpose of this clinical trial is to examine the effect of US-TAP block timing on intraoperative Analgesia Nociception Index (ANI) values—an objective metric of parasympathetic tone—and to determine whether variations in block timing and ANI correlate with postoperative recovery quality, pain scores, and complication rates up to 24 hours postoperatively.

4. Study Methods and Procedures

This study will enroll 120 adult patients aged 19 years or older scheduled for laparoscopic cholecystectomy at our institution. All medications and monitoring devices used—including ropivacaine local anesthetic, standard general anesthetic agents, and the ANI monitor—are approved and routinely employed in standard surgical care.

Participants will be randomized 1:1 into two groups:

Group A (Experimental Group): Receives US-TAP block immediately after general anesthesia induction and prior to surgical skin incision.
Group B (Control Group): Receives US-TAP block immediately after laparoscopic wound closure and prior to emergence from anesthesia.

All regional blocks will be performed by experienced anesthesiologists under sterile conditions using an identical total dose of 30 mL of 0.2% ropivacaine (10 mL lateral TAP, 10 mL subcostal TAP, and 5 mL bilaterally for rectus sheath block). Intraoperative ANI will be monitored continuously. Postoperatively, all patients will receive intravenous patient-controlled analgesia (IV-PCA: fentanyl, nefopam, ramosetron) and will have their pain intensity assessed using the Visual Analogue Scale (VAS) upon PACU arrival, at PACU discharge, and at 12 and 24 hours postoperatively.

5. Randomization Probability

By agreeing to participate, you have an equal chance (1:1 probability, or 50%) of being allocated to Group A (preoperative TAP block) or Group B (postoperative TAP block) via computer-generated randomization.

6. Participant Responsibilities

There are no burdensome additional requirements. You simply need to comply with the standard preoperative fasting guidelines and anesthetic preparation, and participate in routine pain assessments during the 24 hours after surgery.

7. Unproven or Experimental Aspects

Both the US-TAP block and the ANI monitor are already established and widely applied in standard anesthesia and perioperative care. No unapproved drug or experimental device is used in this trial. The sole variable under investigation is the timing of the regional block administration (pre-incision versus post-closure).

8. Foreseeable Risks, Side Effects, and Inconveniences

Participation does not increase the intrinsic risk of anesthesia or surgery beyond standard medical practice. However, you may experience known or unforeseen adverse effects associated with regional anesthesia:
Ropivacaine Local Anesthetic Side Effects: Hypotension, bradycardia, dizziness, headache,

perioral numbness, metallic taste, nausea, or tremors. Severe systemic toxicity (LAST) is extremely rare and will be prevented by strict dose limitation and ultrasound visualization.
TAP Block Procedural Complications: Puncture site hematoma, localized tenderness, transient paresthesia, block failure, or very rarely visceral organ injury.
General Anesthesia Reactions: Allergic or anaphylactoid reactions, transient intraoperative hypotension, or bradycardia (which are promptly corrected with standard rescue drugs such as ephedrine or atropine).

9. Expected Potential Benefits

You will receive high-standard multimodal pain control regardless of your group allocation. While there may be no direct personal therapeutic benefit compared to standard clinical care, the findings of this study will contribute significantly to establishing optimal pain management protocols for future surgical patients.

10. Alternative Treatments

If you choose not to participate, you will still receive standard general anesthesia and postoperative analgesia, which commonly includes ultrasound-guided regional nerve blocks. Declining participation does not change the availability or quality of your clinical pain care.

11. Expected Duration and Number of Participants

The entire study duration spans from IRB approval through June 30, 2027. Your active participation will last for approximately 24 hours after surgery. A total of 120 subjects (60 per group) will be enrolled at Pusan National University Yangsan Hospital.

12. Compensation for Study-Related Injury

Because this study involves established clinical procedures, participation does not entail additional bodily risks beyond standard care. Should unexpected adverse reactions occur, appropriate medical management will be provided in accordance with institutional medical liability protocols. No independent commercial liability insurance is established for this trial.

13. Financial Compensation and Additional Costs

No monetary compensation is provided for participation, and no additional financial costs will be incurred by you as a consequence of taking part in this study.

14. Voluntary Participation and Right to Withdraw

Participation is entirely voluntary. You may decline to participate or withdraw your consent at

any time without penalty or loss of benefits to which you are otherwise entitled. If you choose to withdraw, no further data will be collected without your consent, and your routine clinical care will proceed uninterrupted.

15. Confidentiality and Protection of Personal Data

All data collected—including demographic characteristics, anesthetic records, pain scores, and ANI readings—will be pseudonymized using unique study identification numbers. Your name, hospital ID, and identifying details will remain strictly confidential and will not be disclosed in publications or trial registrations. Trial records will be archived securely for 3 years following study completion and then permanently destroyed in accordance with applicable bioethics laws.

16. Research Contacts and Inquiries

For questions regarding this research study, your rights, or potential study-related complications, please contact:

Principal Investigator: Hyun-Soo Park (Tel: +82-55-360-2129 / +82-10-6715-8812)

Institutional Review Board (IRB) Office: Tel: +82-55-360-3854~5, 4724

Human Research Protection Center Help Desk: Tel: +82-55-360-4725