Study Protocol

With the approval of the XXXXXX Clinical Research Ethics Committee dated 26.12.2023 (No. 2023-172) and registration on ClinicalTrials.gov (NCT06241794), this study commenced. The study was conducted as a prospective, randomized, and blinded trial in the operating rooms of XXXXXXXXXXX Hospital between 01.01.2024 and 01.05.2024. A total of 72 patients, aged 18-65, classified as ASA (American Society of Anesthesiologists) physical status I-II, who were scheduled for laparoscopic cholecystectomy by the general surgery clinic, were included in the study after obtaining written and verbal consent. The study was designed and conducted in accordance with the ethical principles set forth in the Declaration of Helsinki.

Patient randomization was performed using an internet-based software program (Research Randomizer, http://www.randomizer.org/). Patients were randomly assigned to two groups based on the type of nerve block performed:

- Group 1 (n=35): Patients who received a modified thoracoabdominal nerve block via a perichondrial approach (M-TAPA)

- Group 2 (n=37): Patients who received a serratus intercostal plane block combined with a rectus sheath block (SIPB + RSB)

Inclusion criteria:

- Scheduled for laparoscopic cholecystectomy due to cholelithiasis

- ASA physical classification I-II

- Age between 18-65 years

- Body mass index (BMI) <35

- Patients who read and accepted the informed consent form

Exclusion criteria:

- Patients unwilling to participate

- ASA physical classification III or higher

- BMI >35

- Patients unable to score pain using the NRS system

- Patients with allergies to the local anesthetic and analgesic drug used

- Pregnant and breastfeeding patients

- Patients under 18 or over 65 years of age

- Patients with uncontrolled anxiety

- Patients with alcohol and drug addiction

- Patients with neuromuscular diseases and peripheral nerve disorders

- Patients with widespread chronic pain

- Patients with hepatic and renal failure

- Patients with contraindications for peripheral block

- Patients undergoing a second procedure along with laparoscopic cholecystectomy

- Patients with a history of abdominal surgery or trauma

- Patients where laparoscopic surgery was converted to open surgery

- Patients with technical issues using patient-controlled analgesia (PCA) devices

- Patients unable to understand or complete the Quality of Recovery-15 (QoR-15) scale

All necessary information regarding the procedures was provided to the randomized patients, and their written consent was obtained. Patients' ASA status and demographic characteristics (gender, age, height, weight, BMI, chronic diseases) were recorded. Surgeons and postoperative follow-up healthcare workers were not informed of the group assignments, maintaining blinding in the study. Preoperative QoR-15 questionnaires were completed before patients were taken to the operating room. Standard anesthesia monitoring (non-invasive arterial blood pressure measurement, heart rate, electrocardiography, peripheral oxygen saturation measurement) was applied to all patients. A 20G catheter was used to establish a peripheral venous line. The induction of anesthesia was recorded. For premedication, 0.03 mg/kg iv midazolam (Sedozolam, Monemfarma, Istanbul) was administered, and after preoxygenation, anesthesia was induced with 2 mg/kg propofol (Propofol-PF, Polifarma, Tekirdağ) and 1 mcg/kg fentanyl (Fentanyl-PF, Polifarma, Tekirdağ). After administering 0.6 mg/kg iv rocuronium bromide (Jecron, Tüm Ekip İlaç, Istanbul) and achieving muscle relaxation, endotracheal intubation was performed. Mechanical ventilation was provided in pressure-

controlled mode targeting an end-tidal CO2 value of 35-40 mmHg. Anesthesia was maintained with an O2/air mixture (FiO2: 0.40), sevoflurane (Sevorane, AbbVie, Italy) (minimum alveolar concentration 0.8-1), and iv remifentanil (Ultan, Centurion Pharma, Ankara) infusion. The remifentanil infusion was adjusted in the range of 0.01-0.2 mcg/kg/min to keep the patient's mean arterial blood pressure within 20% of the baseline value. The start time of surgery was recorded. In all laparoscopic cholecystectomy operations, standard 4 trocar sites (umbilicus, epigastric region below the xiphoid, and subcostal area within the right midclavicular and right anterior axillary lines) were used. The operation was performed with the patient in the supine position and 30° reverse Trendelenburg position. Pneumoperitoneum was maintained with CO2 insufflation at an intraperitoneal pressure of 12 mmHg. The patient's intraoperative vital signs were monitored according to routine anesthesia protocol.

Thirty minutes before the end of the surgery, all patients received 1 g iv paracetamol (Partemol, Vem ilaç, Tekirdağ), 1 mg/kg tramadol (Tramosel, Haver farma ilaç, Turkey), and 4 mg ondansetron (Laufran, Haver pharma, Tekirdağ). After the completion of the surgery, all block procedures were performed under sterile conditions while the patient was supine under anesthesia. The end time of surgery, end time of anesthesia, time of block performance, and duration from block performance to the end of anesthesia were recorded. All blocks were performed under aseptic conditions.

For the M-TAPA block, USG (Logiq V2, GE, USA) guidance was used to identify the transversus abdominis, internal oblique, and external oblique muscles at the level of the 10th rib in the sagittal plane at the costochondral angle with a linear probe. The probe was angled deeply at the costochondral angle adjacent to the 10th rib to visualize the costal cartilage's inferior surface at the midline. Using an in-plane technique, a 22-G, 80-100 mm block needle (B Braun Stimuplex Ultra, 22 G, 80 mm, Germany) was advanced cranially, directing the needle tip towards the posterior surface of the 10th costal cartilage below the chondrium. Twenty milliliters of 0.25% bupivacaine (Buvasin, VEM ilaç, Turkey, prepared by diluting 10 mL 0.5% with 10 mL saline) was injected under the chondrium. The same procedure was performed on the opposite side.

For SIPB, USG guidance identified the serratus anterior and intercostal muscles at the 8th rib level along the right mid-axillary line. A 22-G, 80 mm block needle was used to inject 20 mL of 0.25% bupivacaine between these muscles. SIPB was performed only on the right side.

For RSB, USG guidance placed a linear probe transversely just above the umbilicus and slightly lateral to the midline. After visualizing the rectus abdominis muscle, posterior rectus sheath, and the hypo-echoic space between them, a 22-G, 80 mm block needle was advanced in-plane through the subcutaneous tissue until the needle tip reached the space between the rectus abdominis muscle's epimysium and the posterior rectus sheath. After negative aspiration, 10 mL of 0.25% bupivacaine was injected. Adequate spread was confirmed by lifting the epimysium of the rectus abdominis muscle while depressing the posterior fascia and peritoneum. The same procedure was performed on the opposite side.

Following the completion of the block procedures, neuromuscular blockade was reversed with 4 mg/kg sugammadex (Brimadex, Polifarma ilaç, Tekirdağ) under 80% O2 ventilation. Patients with adequate spontaneous respiration were extubated and transferred to the recovery room. Patients' vital signs, pain scores, and postoperative nausea and vomiting (PONV) scale were monitored in the recovery room. Pain assessment using the numerical rating scale (NRS) was performed at rest (static) and during active movement (transitioning from lying to sitting - dynamic). Pain intensity was rated from 0 (no pain) to 10 (worst imaginable pain). For postoperative analgesia, iv tramadol PCA was administered. The PCA protocol was set to 10 mg bolus tramadol on demand with a 20-minute lockout period without basal infusion. Tramadol consumption was recorded at 0-1 hour, 0-12 hours, 12-24 hours, and the total at 24 hours. Patients with a pain score above 4 in the recovery room received 25 mcg iv fentanyl as rescue analgesia, which was recorded.

Patients with an Aldrete score of 9 or higher were transferred to the ward. Postoperative pain follow-up was conducted by an anesthetist blinded to the group assignment. NRS scores were recorded at 0, 1, 3, 6, 12, 18, and 24 hours postoperatively. All patients received 1 g iv paracetamol every 8 hours for postoperative analgesia. Patients with pain scores above 4 despite the analgesic regimen received 50 mg iv dexketoprofen (Ketavel, Deva İlaç, Kocaeli) as rescue analgesia.

To determine the sensory block's dermatomal level, pinprick testing was performed at 2 and 24 hours postoperatively using a sterile needle along a vertical line 3-5 cm away from the midline and mid-axillary line between the T3-L1 sensory levels. A three-point numerical scale (0 = no prick sensation, 1 = reduced prick sensation, 2 = normal prick sensation) was used. Scores of 0 or 1 were considered effective. Normal sensation in the shoulder was used for comparison.

Patients were monitored for PONV within the first 24 hours postoperatively using a scale (PONV 1: no nausea or vomiting, PONV 2: nausea but no vomiting, PONV 3: single episode of vomiting or persistent nausea, PONV 4: two or more episodes of vomiting or severe/persistent retching). Patients with a PONV score of 2 or higher received 4 mg iv ondansetron. The total ondansetron dose administered within the first 24 hours postoperatively was recorded.

Patients completed the QoR-15 (Quality of Recovery-15) questionnaire, a self-report measure of postoperative recovery quality, twice: once in the waiting area on the morning of surgery and again 24 hours postoperatively. The time to first oral intake, time to first flatus/stool, and time to first mobilization (standing unaided) within the first 24 hours postoperatively were recorded.

Statistical Methods

The statistical analyses of the data obtained in this thesis were performed using the SPSS software package (Version 22.0, SPSS Inc., Chicago, IL, USA - Licensed by Hitit University). Descriptive statistics were presented as mean ± standard deviation for continuous data showing normal distribution, median (min-max) for continuous data not showing normal distribution, and number and percentage (%) for categorical data. The normality of the data distribution was analyzed using Shapiro-Wilk tests. To compare the means of two independent samples of continuous variables, the independent samples t-test was used for normally distributed data, and the Mann-Whitney U test was used for data not normally distributed. For comparisons of two dependent groups of continuous variables, the paired t-test was applied for normally distributed data. The Friedman test was used for comparing numerical variables among more than two dependent groups with data not normally distributed. After variance analysis, Bonferroni-corrected post-hoc tests were applied to determine the source of differences among groups. Relationships between categorical variables for two independent groups were evaluated using the Chi-square test or Fisher exact test, depending on the cell counts in cross-tabulations. Statistical significance was set at $p<0.05$.