

Analgesic Efficacy of Rectus Sheath Bupivacaine and Intrathecal Morphine With Bupivacaine Compared to Intravenous Patient-controlled Analgesia in Males Undergoing Robot-Assisted Laparoscopic Prostatectomy: A Prospective, Observational Parallel-Cohort Study

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Abstract

Background: We explored the analgesic outcomes on postoperative day (POD) 1 of males undergoing robot-assisted laparoscopic prostatectomy (RALP) who received intravenous (IV) patient-controlled analgesia (PCA), a rectus sheath bupivacaine block (RSB), or an intrathecal morphine with bupivacaine (ITMB) block.

Methods: This was a prospective, observational parallel-cohort trial. Patients were divided into three groups: IV-PCA (n = 30), RSB (n = 30), and ITMB block (n = 30). Peak pain scores at rest and when coughing, cumulative IV-PCA drug consumption, the need for IV rescue opioids, and Quality of Recovery-15 (QoR-15) questionnaire scores collected on POD 1 were compared among the groups.

Results: The preoperative and intraoperative findings were comparable among the groups; the ITMB block group required the least remifentanyl of all groups. During POD 1, the ITMB block group reported lower levels of pain at rest and when coughing than did the other two groups. After adjustment for age, body mass index, comorbidities, and intraoperative remifentanyl infusion, severe pain at rest was 0.167-fold less common in the ITMB block than in the IV-PCA group, and pain when coughing was 0.1-fold lower in the ITMB block group and 0.306-fold lower in the RSB group compared to the IV-PCA group. The ITMB block group required lower cumulative IV-PCA drug infusions and less IV rescue opioids, and exhibited a better QoR-15 global score than did the other two groups.

Conclusion: An ITMB block seems to provide appropriate analgesia with tolerable complications and enhances early patient recovery after RALP.

Trial registration: Clinical Research Information Service, Republic of Korea, (approval number: KCT0005040) on May 20, 2020

https://cris.nih.go.kr/cris/search/search_result_st01_kren.jsp?seq=15943&sLeft=2<ype=my&rtype=my

Background

Robot-assisted laparoscopic prostatectomy (RALP) is a technically advanced, minimally invasive surgical method affording a much better surgical view and greater maneuverability than open or laparoscopic prostatectomy [1]. Previous studies found that RALP was associated with better oncological and functional outcomes than open or laparoscopic radical prostatectomy [2, 3]. However, RALP patients frequently experience considerable pain, particularly on the day after surgery, reflecting the skin-port incisions, multiple dissections of prostate-involved and surrounding tissues, bladder spasm, and transurethral catheter irritation [4]. Various central and/or peripheral pain-relief methods have been used to attenuate the severe pain that develops immediately after RALP [5, 6]. A rectus sheath block (RSB) afforded peri-umbilical incision site analgesia superior to that achieved via local anesthetic infiltration; this site is the principal source of pain immediately after laparoscopy-based surgery [7]. Compared to a transversus abdominis plane (TAP) block, a RSB may afford better analgesia when a midline incision is

created and more prolonged blockade of noxious input from that site [8]. An intrathecal morphine and bupivacaine (ITMB) block afforded pain relief for 20–48 h postoperatively and reduced bladder spasm-related discomfort (a common complication associated with urinary catheter insertion after prostate surgery) [9]. However, no ideal analgesic method affording maximal benefits with minimal side effects has been described; this would improve the quality of early postoperative recovery after RALP.

Here, we measured the analgesic outcomes on postoperative day (POD) 1 of males undergoing RALP who received an RSB or ITMB block compared to those on intravenous patient-controlled analgesia (IV-PCA) alone. We also compared postoperative complications, including patient satisfaction.

Methods

Ethical considerations

This was a prospective, observational parallel-cohort trial. The protocol was approved by the Institutional Review Board of Seoul St. Mary's Hospital Ethics Committee (approval no. KC200ISI0124) on April 29, 2020. The study was performed in accordance with all relevant principles of the Declaration of Helsinki. The study protocol was prospectively registered on a publicly accessible clinical registration site recognized by the International Committee of Medical Journal Editors (Clinical Research Information Service, Republic of Korea; approval no. KCT0005040) on May 20, 2020. Written informed consent was obtained from all patients enrolled between May and July, 2020. The study adhered to Strengthening the Reporting of Observational Studies in Epidemiology guidelines (Additional File 1); a study flow chart is shown in Figure 1.

Study population

The inclusion criteria for our study were: male sex, age 19–74 years, prostate cancer stage I or II [10], patients scheduled for elective RALP, and American Society of Anesthesiologists (ASA) physical status I or II. The exclusion criteria were: a history of allergy to a local anesthetic or opioid drug, coagulopathy (international normalized ratio [INR] >2.0 and platelet count $<100.0 \times 10^9/L$), hemodynamic instability that required strong vasopressors or a blood product transfusion, and refusal to participate.

We divided the patients into three groups based on patient preference: IV-PCA only (reference group), RSB and IV-PCA (RSB group), and ITMB and IV-PCA (ITMB group).

Patient management in the operating room

The RALP surgical technique and balanced anesthetic management were as described previously [11]; patient care was standardized apart from the analgesic treatments. The attending anesthesiologist and nurses were aware of the group allocations but were not involved in later patient care or data collection (other than the completion of medical records). The RSB was established immediately after the induction of general anesthesia. An ultrasound probe was positioned transversely on the rectus abdominis muscle,

above the umbilicus (Figure 2). Guided by real-time ultrasound, a sterile 22-G Tuohy-type epidural needle was cautiously advanced in-plane (to prevent injury to nearby vessels) from medially to laterally until the tip attained the plane between the lateral side of the rectus abdominis muscle and the posterior rectus sheath. After negative pressure aspiration, 20 mL of 0.25% (w/v) bupivacaine was administered and the block repeated on the opposite side. The ITMB block was placed before the induction of general anesthesia. Each patient received 0.2 mg of intrathecal morphine sulfate and 7.5 mg of bupivacaine via a sterile 25 G Quincke type spinal needle inserted between lumbar vertebrae 3 and 4. The drugs were given via a single injection after cerebrospinal fluid was collected. All patients were allowed access to IV-PCA (1,000 µg of fentanyl, 90 mg of ketorolac, and 0.3 mg of ramosetron). The IV-PCA program featured a 2-mL bolus injection and 0.5-mL basal infusion with a lockout time of 10 min. If a patient suffered acute postoperative breakthrough pain (visual analog scale [VAS] score ≥ 7), 25 mg of pethidine (an IV rescue opioid) was administered based on the discretion of the attending physicians (in the postoperative acute care unit or ward), who were blinded to group assignment.

Pain outcomes

Over the first postoperative 24 h, peak pain scores when resting and coughing were assessed using a VAS ranging from 0 to 10, where “0” represented no pain and “10” the worst possible pain; pain severity was classified as mild (VAS scores 0–3), moderate (4–6), and severe (7–10). Cumulative IV-PCA drug consumption and the need for IV rescue opioids were assessed.

Clinical variables

Preoperative demographic and laboratory parameters were recorded. Intraoperative findings included surgical duration, hypotension status (systolic blood pressure < 90 mmHg for more than 10 min), total rescue ephedrine infusion, total remifentanyl infusion, crystalloid fluid infusion, urine output, and hemorrhage status. Postoperative findings included the global quality-of-recovery score on a 15-item questionnaire (the QoR-15) [12]; the incidences of nausea, vomiting, and pruritus; the Clavien-Dindo classification [13]; and laboratory variables.

Statistical analyses

The minimum sample size was based on the difference in cumulative IV opioid consumption on POD 1 between patients who received the RSB and ITMB block, calculated using electronic medical records. A minimum sample size of 27 patients/group was required to afford an $\alpha = 0.05$ and a power of 0.8. We recruited 30 patients for each group; we assumed a dropout rate of 10%. Data are expressed as means \pm standard deviations (SDs), medians with interquartile ranges (IQRs), or numbers with proportions (%), as appropriate. The normality of continuous data distributions was evaluated using the Shapiro-Wilk test. Continuous perioperative variables of the three groups were compared via a one-way analysis of variance or the Kruskal-Wallis test; *post-hoc* testing employed the unpaired *t*-test or the Mann-Whitney U test. Perioperative categorical variables were compared among the groups using the Pearson χ^2 test or Fisher exact test, as appropriate. Trend testing employed a linear-by-linear association method. Logistic

regression analysis was used to derive odds ratios with 95% confidence intervals of the risks (postoperative VAS score peaks ≥ 7 at rest and when coughing) associated with IV-PCA alone (reference), and the RSB and ITMB block, after adjusting for age, body mass index, diabetes mellitus and hypertension status, and intraoperative remifentanyl consumption. All tests were two-sided and a p -value < 0.017 was considered significant (multiple comparisons were made). All statistical analyses were performed with the aid of SPSS for Windows (ver. 24.0; IBM Corp., Armonk, NY, USA) and MedCalc for Windows (ver. 11.0; MedCalc Software, Ostend, Belgium).

Results

Study population

A total of 103 patients were assessed in terms of eligibility. Thirteen aged > 74 years ($n = 6$), of ASA physical status III ($n = 5$), or who refused to participate ($n = 2$) were excluded. Thus, 90 patients were enrolled and divided into 30 in each of the IV-PCA, RSB, and ITMB block groups.

Preoperative and intraoperative findings

Of all patients ($n = 90$), the median age was 65 (62–71) years and the median body mass index 24.0 (22.5–26.5) kg/m^2 . In total, 15 patients (16.7%) had diabetes mellitus and 35 (38.9%) hypertension. Table 1 shows that the preoperative and intraoperative findings were comparable among the three groups. However, during surgery, the ITMB block group exhibited the lowest remifentanyl consumption, and the RSB group required less remifentanyl than the IV-PCA alone group.

Postoperative pain

During POD 1, the ITMB block group reported lower pain levels at rest and when coughing than did the RSB and IV-PCA groups (Figure 3). After adjustment for age, body mass index, comorbidity status, and intraoperative remifentanyl infusion, the severe pain level at rest was 0.167-fold lower in the ITMB block group than in the IV-PCA group, and that during coughing was 0.1-fold lower in the ITMB and 0.306-fold lower in the RSB group compared to the IV-PCA alone group (Table 2). The ITMB block group required less IV-PCA drug infusion and IV rescue opioids than did the RSB and IV-PCA groups (Table 3).

Postoperative clinical findings

The global QoR-15 questionnaire score was higher in the ITMB block than the RSB and IV-PCA groups (Table 3). Complications (nausea and pruritus) were marginally more common in the ITMB block group than the other two groups; however, we noted no ITMB block- or RSB-related surgical complication (Clavien-Dindo class I or II) (respiration depression, post-dural headache, nerve injury, or puncture site hematoma or infection) during the hospital stay.

Discussion

Our principal findings are that the ITMB block afforded superior analgesia and better patient satisfaction (in terms of early postoperative recovery) compared to the RSB in males undergoing RALP. The analgesic efficacy of the ITMB block was approximately three-fold better (in terms of reducing severe pain during the early postoperative period) than that of the RSB. Although the ITMB block was associated with more nausea and pruritus than the RSB, we noted no ITMB block-related, postoperative adverse event (respiration depression, lower leg numbness, or post-dural puncture headache).

One retrospective study comparing intrathecal and peripheral postoperative blocks for patients, including those undergoing robotic pancreatoduodenectomy, suggested that intrathecal morphine administration was significantly associated with a lower pain score and a lower opioid requirement soon after surgery than were a tap block and a quadratus lumborum nerve block [14]. In an orthopedic study, intrathecal morphine seemed to be more reliable in terms of analgesic efficacy and opioid-sparing than a femoral nerve block [15]. In a gynecological study, the addition of intrathecal bupivacaine to intrathecal morphine significantly improved postoperative pain relief, but the addition of rectus sheath bupivacaine to intrathecal morphine did not afford additional analgesia [16]. A urological study suggested that multimodal pain control via intrathecal bupivacaine/morphine may optimally improve the quality of early recovery and reduce postoperative pain, being associated with less pain during exertion and fewer bladder spasms (compared to a control group) [5]. Our ITMB block data are similar to those of previous laparoscopic or open surgery reports [5, 14–16]; the ITMB block was a feasible and practicable form of pain relief, not associated with serious complications (such as nerve injury) during or after surgery, and was better than the RSB or IV-PCA alone.

The differences between intrathecal and peripheral blocks include the sites affected by the analgesic drugs and later drug actions. Intrathecally injected morphine and bupivacaine become widely dispersed in cerebrospinal fluid, thus more reliably (than the RSB) preventing nociceptive inputs from multiple somatic dermatomic levels of patients undergoing RALP [16, 17]. The principal skin wound created during laparoscopy-based surgery lies in the peri-umbilical area; the orifice is used for camera insertion and specimen (prostate mass) removal. In the past, an RSB effectively countered pain caused by injury to the peri-umbilical dermatomes [18, 19]. However, as surgery advanced from open surgery to human-executed laparoscopic surgery to RALP (reducing the operation time and numbers of painful stimuli delivered by surgical wounds in sites such as the umbilicus) [20], the analgesic effect of an RSB seems to have gradually decreased as surgical wound care techniques also improved. Also, an ITMB block may deliver visceral analgesia by interacting with spinal μ - and κ -opioid receptors and voltage-gated sodium channels that contain binding sites for local anesthetics. It is now possible to totally (and simultaneously) avoid the surgical stress and pain imparted by intra-abdominal wounds (created when prostate-adjacent tissues are dissected and retracted) and skin wounds (created when the skin is incised, punctured, and retracted) [21, 22]. However, the RSB blocks only somatic, afferent nerve pain, and thus cannot deliver comprehensive analgesia; pain from the visceral origins is not dulled [18].

Turning to complications, postoperative nausea/vomiting and pruritus compromise the quality of patient recovery [23]. Previous studies suggested that the incidence of such complications was higher in patients

who received intrathecal morphine than in those receiving local anesthetic-based analgesia [24–26]. Our ITMB block regimen included bupivacaine (7.5 mg); this allowed us to reduce the morphine dose to 0.2 mg, in turn reducing nausea/vomiting and pruritus but with maintenance of appropriate analgesia. We found no significant difference in the incidences of nausea and vomiting among patients who received the ITMB block, the RSB, and IV-PCA alone. Nguyen *et al.* [27] suggested that the addition of bupivacaine (15 mg) to intrathecal morphine (0.4 mg) improved pain relief and reduced the incidence of adverse events (such as hypotension) in patients undergoing laparoscopic liver resection. Girgin *et al.* [28] found that the incidence of pruritus increased as the dose of intrathecal morphine rose from 0.1 to 0.4 mg; however, when morphine was combined with low-dose bupivacaine (7.5 mg), the complication rate was reduced but analgesia remained stable in women undergoing Cesarean sections. The good analgesia, and the tolerable complication rate, afforded by the ITMB block may enhance early postoperative recovery compared to that of patients treated via the RSB and IV-PCA alone.

Our work has certain limitations. First, we (obviously) included only males. As opioid-related analgesia and side effects vary by sex [29], further work is required to investigate the quality of postoperative recovery, including pain, afforded by the various analgesic methods in both males and females. Second, we delivered single bupivacaine injections to the rectus sheath when comparing the outcomes of the three pain relief methods. However, no ideal regional analgesic technique for RALP has yet been established; other regional analgesic models, including catheter-delivered continuous blockade, may be even better than the ITMB block [30].

Conclusions

The ITMB block may usefully reduce postoperative pain and aid recovery in males undergoing RALP. Although robot-assisted surgery is more advanced and less invasive than open or laparoscopic surgery, analgesic care must counter both parietal and visceral pain associated with multi-level skin wounds and intra-abdominal tissue injuries. Our ITMB block regimen (a low dose of morphine combined with bupivacaine) seems to deliver appropriate analgesia with a tolerable level of complications, and to enhance early patient recovery.

Abbreviations

RALP, Robot-assisted laparoscopic prostatectomy; RSB, rectus sheath block; TAP, transversus abdominis plane block; ITMB, intrathecal morphine and bupivacaine block; POD, postoperative day; IV-PCA, Intravenous patient-controlled analgesia; ASA, American Society of Anesthesiologists; INR, international normalized ratio; VAS, visual analogue scale; QoR-15, quality-of-recovery score on a 15-item questionnaire

Declarations

Ethics approval and consent to participate

This was a prospective, observational parallel-cohort trial. The protocol was approved by the Institutional Review Board of Seoul St. Mary's Hospital Ethics Committee (approval no. KC200ISI0124) on April 29, 2020. The study was performed in accordance with all relevant principles of the Declaration of Helsinki. The study protocol was prospectively registered on a publicly accessible clinical registration site recognized by the International Committee of Medical Journal Editors (Clinical Research Information Service, Republic of Korea; approval no. KCT0005040) on May 20, 2020. Written informed consent was obtained from all patients enrolled between May and July, 2020. The study adhered to Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to declare.

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Authors' contributions

J.W.S. and M.S.C. designed the study, wrote the manuscript, and analyzed and interpreted the data. J.W.S., Y.J.C., M.K., S.H.H., H.W.M., S.H.H. and M.S.C. collected the data and provided critical comments. All authors revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Tables

Table 1
Comparisons of preoperative and intraoperative findings between the three groups

Group	IV-PCA	RSB	ITMB	
n	30	30	30	p
Preoperative findings				
Age (years)	65 (61–69)	67 (64–72)	65 (62–71)	0.286
Body mass index (kg/m ²)	24.4 (22.7–27.7)	23.6 (22.2–25.2)	24.2 (22.3–26.4)	0.276
<i>Comorbidity</i>				
Hypertension	9 (30.0%)	10 (33.3%)	16 (53.3%)	0.134
Diabetes mellitus	7 (23.3%)	3 (10.0%)	5 (16.7%)	0.383
History of abdominal surgery	7 (23.3%)	4 (13.3%)	6 (20.0%)	0.602
<i>Laboratory variables</i>				
White blood cell count (x 10 ⁹ /L)	5.4 (4.6–7.4)	7.1 (5.9–7.6)	6.2 (5.2–7.5)	0.133
Neutrophil (%)	54.3 (47.9–57.2)	55.1 (51.6–59.6)	52.9 (51.1–54.5)	0.118
Lymphocyte (%)	33.8 (31.3–38.3)	32.6 (31.1–40.4)	36.5 (34.6–39.0)	0.089
Hemoglobin (g/dL)	14.3 (13.8–14.8)	13.9 (13.1–15.4)	14.7 (13.7–15.6)	0.375
Platelet count (x 10 ⁹ /L)	187.0 (160.5–221.0)	193.0 (169.8–242.0)	207.0 (172.3–232.3)	0.52
International normalized ratio	0.9 (0.8–0.9)	0.9 (0.9–0.9)	0.9 (0.8–0.9)	0.148
Intraoperative findings				
Surgical duration (min)	123 (109–145)	123 (100–141)	123 (114–138)	0.713
Hypotension event [§]	10 (33.3%)	15 (50.0%)	17 (56.7%)	0.175
Total rescue ephedrine infusion (mg)	0 (0–4)	2 (0–8)	4 (0–8)	0.139
Total remifentanil infusion (mg)	0.5 (0.4–0.6)	0.4 (0.3–0.4)*	0.2 (0.1–0.3)* [†]	< 0.001
Crystalloid fluid infusion (mL)	500 (400–600)	575 (400–663)	525 (388–800)	0.782
Urine output (mL)	100 (50–100)	50 (50–100)	100 (50–100)	0.496
Hemorrhage (mL)	100 (50–100)	100 (50–100)	100 (50–163)	0.405

Group	IV-PCA	RSB	ITMB
Abbreviations: IV-PCA, intravenous patient-controlled analgesia; VAS, visual analog scale; PACU, post-anesthesia care unit			
* $p < 0.017$ as statistical significance based on the level in the IV-PCA group			
† $p < 0.017$ as statistical significance based on the level in the RSB group			
§Hypotension event defined as systolic blood pressure < 90 mmHg over 10 min			
NOTE: Values are expressed as the median (interquartile) and number (proportion).			

Table 2

Analgesic efficacy of IV-PCA, the RSB, and ITMB block with severe pain (peak VAS ≥ 7) at rest and cough during 24 h postoperatively

	β	Odds ratio	95% Confidence interval	p
Severe pain at rest				
Analgesia adjusted for age, BMI, DM, hypertension, and intraoperative remifentanil consumption				
IV-PCA	Reference			
RSB	-0.74	0.477	0.156–1.464	0.196
ITMB	-1.792	0.167	0.041–0.675	0.012
Severe pain at cough				
Analgesia adjusted for age, BMI, DM, hypertension, and intraoperative remifentanil consumption				
IV-PCA	Reference			
RSB	-1.186	0.306	0.105–0.888	0.029
ITMB	-2.303	0.1	0.029–0.34	< 0.001
Abbreviation: VAS, visual analog scale; IV-PCA, intravenous patient-controlled analgesia; RSB, rectus sheath block; ITMB, intrathecal morphine with bupivacaine; BMI, body mass index; DM, diabetes mellitus				

Table 3
Comparisons of patient outcomes during the first 24 h postoperatively between the three groups

Group	IV-PCA	RSB	ITMB	p
n	30	30	30	
<i>Requirement of opioid infusion</i>				
Cumulative IV-PCA infusion (mL)	37.6 (25.9–57.3)	42.8 (29.9–60.8)	18.7 (14.7–26.2) ^{*,†}	< 0.001
IV rescue opioid infusion	19 (63.3%)	21 (70.0%)	6 (20.0%) ^{*,†,‡}	< 0.001
<i>Quality of early recovery</i>				
Global score of QoR-15 questionnaire on POD 1	124 (122–129)	124 (117–133)	130 (126–141) ^{*,†}	0.002
<i>Complications</i>				
Nausea	2 (6.7%)	2 (6.7%)	9 (30.0%) [‡]	0.012
Vomiting	0 (0.0%)	1 (3.3%)	2 (6.7%)	0.355
Pruritus	0 (0.0%)	0 (0.0%)	5 (16.7%) [‡]	0.005
<i>Laboratory variables on POD 1</i>				
White blood cell count (x 10 ⁹ /L)	13.5 (8.7–16.5)	15.4 (8.2–20.7)	14.3 (11.2–19.3)	0.478
Neutrophil (%)	172.0 (141.0–203.3)	175.5 (154.0–211.8)	168.0 (151.3–201.0)	0.873
Lymphocyte (%)	73.5 (69.1–76.5)	73.1 (68.0–78.7)	71.4 (65.1–78.9)	0.807
Hemoglobin (g/dL)	8.8 (7.4–11.0)	7.8 (7.1–9.1)	8.7 (6.6–10.3)	0.476
Platelet count (x 10 ⁹ /L)	12.6 (11.7–13.4)	12.2 (11.0–13.5)	12.3 (11.7–12.9)	0.419
International normalized ratio	1.0 (0.8–1.0)	0.9 (0.9–1.0)	0.9 (0.8–1.0)	0.072
Abbreviations: QoR-15, Quality of Recovery-15 questionnaire; POD, postoperative day				
* <i>p</i> < 0.017 as statistical significance based on the level in the IV-PCA group				
† <i>p</i> < 0.017 as statistical significance based on the level in the RSB group				
‡ <i>p</i> < 0.05 using the linear-by-linear method				
NOTE: Values are expressed as the median (interquartile) and number (proportion).				

Figures

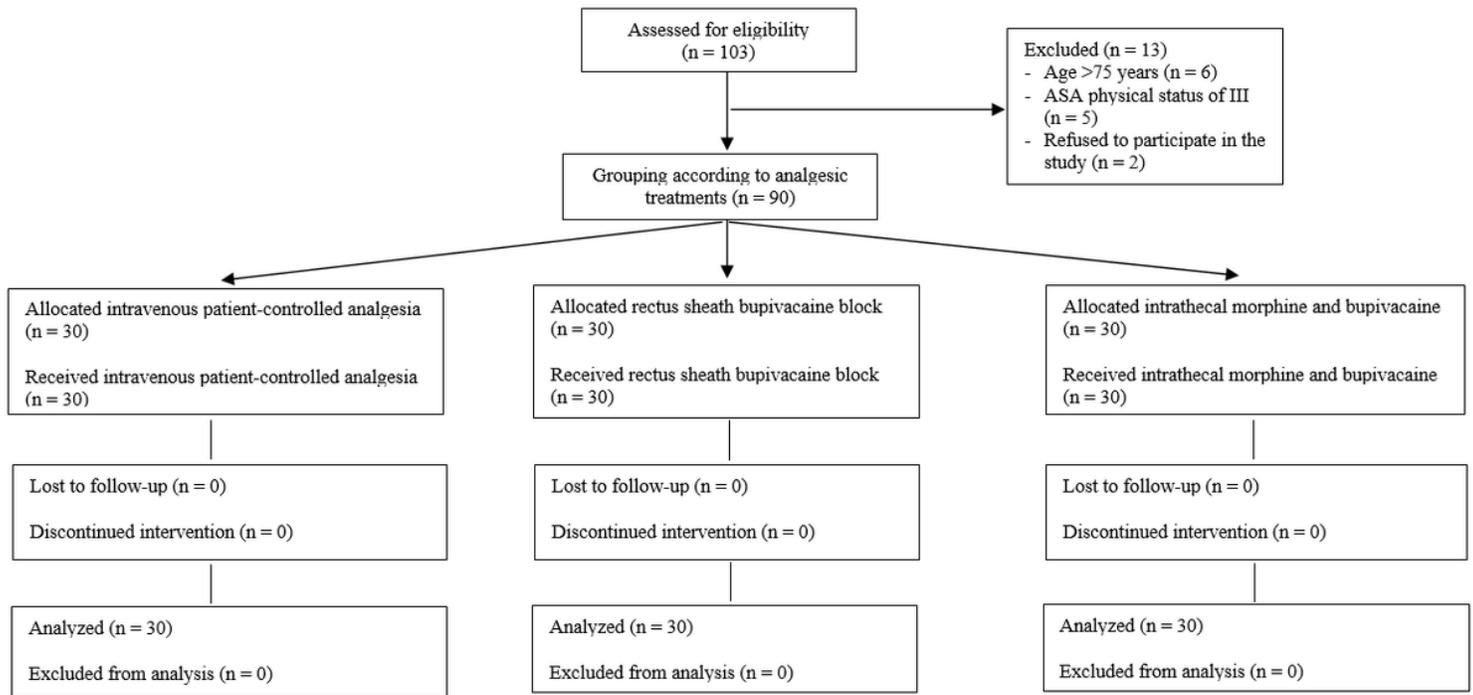


Figure 1

A flow chart of the study

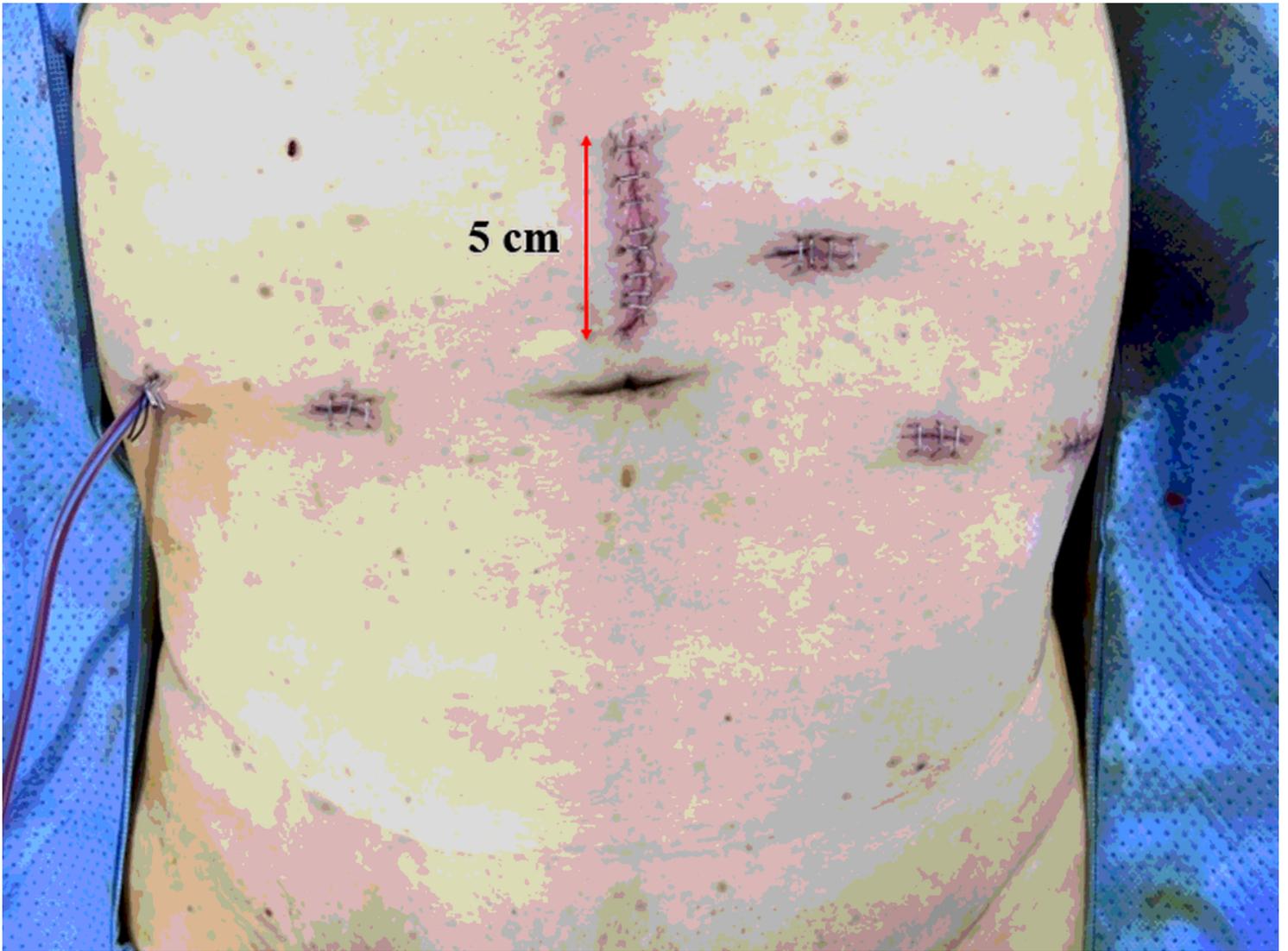


Figure 2

The peri-umbilical wound site (arrow) that is the principal analgesic target of the RSB.

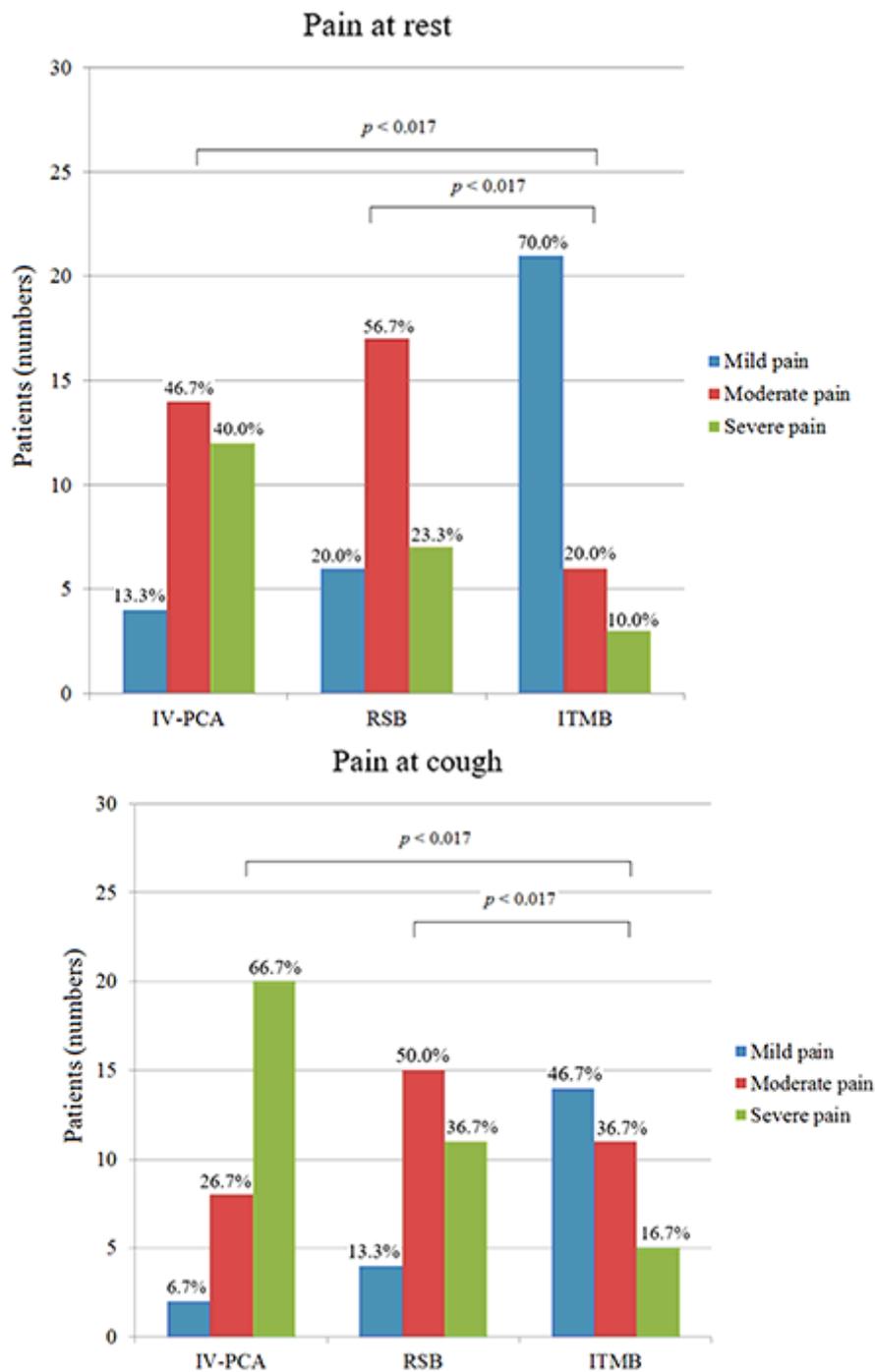


Figure 3

Pain scores (A) at rest and (B) during coughing of the three groups (each n = 30) in the first postoperative 24 h. Mild pain was defined as a peak VAS score of 0–3, moderate pain as a peak score of 4–6, and severe pain as a peak score of 7–10. $p < 0.017$ indicates statistical significance (adjusted for multiple comparisons). Values are expressed as numbers with proportions (% values).

Supplementary Files

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