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Dexmedetomidine-Adjunct Erector Spinae Plane Block: Cortisol Response and Quality of Recovery After Major Gynecologic Surgery

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ABSTRACT: Background: Dexmedetomidine as an adjuvant to erector spinae plane (ESP) block has demonstrated analgesic benefits, but its relationship with postoperative stress biomarkers and early recovery in major abdominal gynecologic surgery remains insufficiently characterized. This study evaluated the effects of dexmedetomidine added to ESP block on postoperative pain, rescue opioid requirements, cortisol, systemic immune-inflammation index (SII), and Quality of Recovery-15 (QoR-15).

Methods: This single-blind randomized controlled trial included 38 patients undergoing major abdominal gynecologic surgery. Participants received bilateral ultrasound-guided ESP block with levobupivacaine 0.25% alone or with dexmedetomidine 0.5 μg/kg. Pain intensity, cortisol, and SII were assessed at the prespecified time points, rescue opioid requirements were recorded, and QoR-15 was assessed preoperatively and 24 hours after surgery. Between-group comparisons and multivariable linear regression were performed.

Results: At 24 hours, low pain was observed in all patients receiving ESP–dexmedetomidine versus 31.6% with ESP alone ($p < 0.001$). Rescue opioid requirements were significantly lower in the combination group ($p < 0.001$). Cortisol and SII levels were lower at 12 and 24 hours postoperatively. Good recovery was achieved in 57.9% versus 10.5% of patients, respectively ($p < 0.001$). Multivariable analysis showed that postoperative cortisol and pain intensity were independently associated with QoR-15, whereas SII was not.

Conclusion: Adding dexmedetomidine to the ESP block was associated with improved early postoperative analgesia, lower postoperative cortisol and SII values, and a more favorable distribution of QoR-15 recovery categories.

1. INTRODUCTION

Major abdominal gynecologic surgery, including abdominal hysterectomy and myomectomy, is commonly performed and is associated with substantial postoperative pain. Inadequately controlled pain may impair early mobilization, increase opioid consumption, prolong hospitalization, and compromise recovery. In Indonesia, most patients undergoing major abdominal gynecologic surgery experience mild-to-moderate pain during the first 24 hours postoperatively.(Wu et al., 2020) The Numeric Rating Scale (NRS) is widely used to assess acute postoperative pain because of its reliability and sensitivity to clinical changes.(Hjermstad et al., 2011; Chou et al., 2016)

Effective analgesia is an important component of Enhanced Recovery After Surgery (ERAS), while opioid-related adverse effects have increased the need for multimodal and regional analgesia.(Chou *et al.*, 2016; Ljungqvist *et al.*, 2017) The erector spinae plane (ESP) block provides broad somatic and visceral analgesia through local anesthetic deposition in the interfascial plane and has a favorable safety profile.(Forero et al., 2016; Adhikary et al., 2018) However, the duration and quality of analgesia may require optimization. Dexmedetomidine, a selective α2-adrenergic agonist, has analgesic and sympatholytic properties and may prolong sensory blockade and reduce postoperative pain and opioid requirements.(Choi et al., 2022)

The clinical impact of surgery extends beyond pain to neuroendocrine and inflammatory responses. Surgical stress activates the hypothalamic–pituitary–adrenal axis and increases cortisol, which reflects the magnitude of surgical stress and is associated with postoperative pain and systemic inflammation.(Tazreean *et al.*, 2022) Regional analgesia may attenuate this response, while dexmedetomidine may further reduce perioperative cortisol through its sympatholytic effects.(Kehlet, 1997; Shamim et al., 2017) Surgical trauma also induces systemic inflammation, which can be assessed using the Systemic Immune-Inflammation Index (SII), a composite marker derived from platelet, neutrophil, and lymphocyte counts.(Smajic et al., 2018; Chen et al., 2025)

Because postoperative recovery is multidimensional, assessment should extend beyond pain and physiological markers. The Quality of Recovery-15 (QoR-15) evaluates physical comfort, emotional and psychological function, social support, and pain, while postoperative opioid consumption provides an objective indicator of analgesic effectiveness.(Andersen et al., 2017; Myles et al., 2022) Thus, an analgesic strategy capable of improving pain control while attenuating stress and inflammatory responses and reducing opioid requirements may provide more comprehensive recovery benefits.

Despite accumulating evidence supporting dexmedetomidine as an adjuvant to local anesthetics in erector spinae plane (ESP) block, important questions remain regarding the relationship between its clinical analgesic effects, perioperative stress responses, and early postoperative recovery in patients undergoing major abdominal gynecologic surgery. Previous studies have primarily emphasized pain intensity, rescue analgesic requirements, and the duration of analgesia, whereas the extent to which changes in neuroendocrine and systemic inflammatory markers accompany improvements in patient-reported recovery remains less clearly characterized in this specific surgical population. Cortisol provides an indirect measure of the neuroendocrine stress response, while the SII reflects changes in circulating neutrophils, platelets, and lymphocytes. However, these markers represent different biological domains and may not contribute equally to the patient's overall recovery experience. In particular, whether postoperative cortisol and SII are independently associated with early recovery after accounting for pain intensity remains an important question.

Accordingly, the present randomized controlled trial evaluated the effects of adding dexmedetomidine to levobupivacaine in bilateral ESP block on postoperative pain intensity, opioid rescue requirements, perioperative cortisol concentrations, SII, and Quality of Recovery-15 (QoR-15) in patients undergoing major abdominal gynecologic surgery. Beyond assessing between-group differences in clinical and laboratory outcomes, the study explored the independent associations of postoperative cortisol, SII, and pain intensity with early postoperative recovery. By examining these outcomes within the same clinical study, this investigation sought to characterize the relationship between perioperative stress-related markers and patient-reported recovery, rather than to establish a specific molecular mechanism of dexmedetomidine.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This prospective analytical experimental study employed a single-blind randomized controlled trial (RCT) design and was conducted at the Central Operating Theatre and inpatient wards of Dr. Moewardi Hospital, Surakarta, Indonesia. Participant recruitment was conducted from July 2026 until August 2026. The study protocol was approved by the Health Research Ethics Committee of Universitas Hasanuddin/Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia (Ethics Approval No. 863/UN4.6.4.5.31/PP36/2026; approved on 14 July 2026). Written informed consent was obtained from all participants before enrollment.

2.2 Participants

The study population consisted of patients undergoing major abdominal gynecologic surgery at Dr. Moewardi Hospital. Participants were recruited consecutively according to predefined eligibility criteria. Eligible patients were aged 18–60 years,

had American Society of Anesthesiologists (ASA) physical status I–II, were scheduled for major abdominal gynecologic surgery under general anesthesia, and had no contraindication to peripheral regional anesthesia. Patients were excluded if they had contraindications to regional anesthesia, hypersensitivity to the study medications, coagulopathy, uncontrolled hypertension, ischemic heart disease, renal dysfunction, pre-existing neurological deficits, or psychiatric disorders. Patients were withdrawn from the study if they developed anesthetic or surgical complications or voluntarily discontinued participation.

2.3 Sample Size and Randomization

The sample size was calculated based on the primary outcome, the QoR-15 score. Assuming a pooled standard deviation of 10 points and a clinically meaningful between-group difference of 8 points, the minimum required sample size was 19 participants per group, yielding a total of 38 participants. Eligible patients were consecutively enrolled and individually randomized in a 1:1 ratio to receive either a standard ESP block or an ESP block with dexmedetomidine using simple, unrestricted randomization without blocking or stratification. The random allocation sequence was generated using computer-generated random numbers, and allocation was concealed using sealed envelopes opened only after participant enrollment. The anesthesiologist who prepared and performed the block could not be blinded because the two solutions differed in composition. However, participants were not informed of their assigned intervention, and the outcome assessor responsible for recording numerical rating scale NRS pain scores, rescue opioid consumption, and QoR-15 scores was blinded to group allocation; therefore, the trial was considered single-blind. The final sample comprised 38 participants, with 19 allocated to each group. The sample size calculation was based exclusively on QoR-15, whereas pain scores, opioid consumption, cortisol levels, and the SII were treated as secondary, exploratory outcomes.

2.4 Anesthetic and ESP Block Procedures

All participants received standardized general anesthesia per departmental protocol. Neuraxial anesthesia and other interfascial blocks were not permitted. Standard perioperative monitoring included electrocardiography, non-invasive blood pressure, and peripheral oxygen saturation, with end-tidal carbon dioxide monitoring when indicated. Following surgery, participants received bilateral ultrasound-guided ESP blocks at the T9–T10 level. In the standard ESP group, levobupivacaine 0.25% (20 mL per side) was injected into the interfascial plane between the erector spinae muscle and the transverse process. In the intervention group, dexmedetomidine 0.5 μg/kg body weight was added to the levobupivacaine solution and administered using the same ESP block technique. Ultrasound visualization was used to confirm longitudinal spread of the injectate within the interfascial plane, with a targeted sensory distribution from T6 to T12.

2.5 Outcome Measurements

Pain intensity was assessed using the Numeric Rating Scale (NRS), ranging from 0 to 10, with 0 indicating no pain and 10 representing the worst pain imaginable. Patients were asked to rate their pain based on their subjective perception at 12 and 24 hours after surgery. Time zero for postoperative time points was the end of surgery. For categorical analyses, NRS scores were classified as low (0–3), moderate (4–6), or high (7–10) pain. Higher NRS scores indicated greater pain intensity. Rescue analgesia was administered according to the study protocol when the NRS score was ≥4, using intravenous fentanyl at 0.5–1 μg/kg, titrated according to the patient's clinical response. The time to first rescue analgesic administration was also recorded. The rescue protocol was applied identically in both groups: an intravenous fentanyl bolus of 0.5 μg/kg was administered when the NRS pain score was >6 and was given to all participants by a non-researcher anaesthesiologist. Because rescue fentanyl was triggered by the NRS score, pain scores and opioid consumption are interdependent outcomes.

Serum cortisol was assessed as a biomarker of the physiological stress response to surgery. Peripheral venous blood samples were collected and analyzed in the clinical laboratory to determine cortisol concentrations, expressed in micrograms per deciliter (μg/dL). Cortisol measurements were intended to evaluate perioperative stress responses and to compare the effects of the two ESP block regimens. Venous blood samples were collected at three time points: preoperatively and at 12 and 24 hours after surgery.

The SII was calculated using peripheral blood platelet, neutrophil, and lymphocyte counts according to the following formula: SII = (Platelet count × Neutrophil count) / Lymphocyte count. The index was used to evaluate the systemic inflammatory and immune response following surgery. Blood samples were collected for complete blood count analysis, and the resulting SII values were compared between the standard ESP block group and the dexmedetomidine-adjuvant group. Complete blood counts for SII were obtained from the same venous samples at the same three time points.

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Postoperative opioid consumption was defined as the total amount of intravenous fentanyl administered during the first 24 hours after surgery. Both groups received the same standard multimodal analgesic regimen consisting of paracetamol 1 g every 8 hours, with intravenous fentanyl available as rescue analgesia according to the study protocol. Total fentanyl consumption was recorded in micrograms (μg), together with the time of the first rescue analgesic administration.

Postoperative recovery was evaluated using the Quality of Recovery-15 (QoR-15) questionnaire, a 15-item patient-reported outcome measure assessing physical comfort, emotional state, psychological support, physical independence, and pain. The total score ranges from 0 to 150, with higher scores indicating better postoperative recovery. The questionnaire was completed independently by patients or administered through a standardized interview when necessary. QoR-15 was administered at two time points: preoperatively (baseline) and 24 hours after surgery. For categorical analysis, a total score of ≥118 was classified as good recovery and a score of <118 as poor recovery. This dichotomy is a study-specific classification; it is not a universally established threshold, and dichotomizing a continuous score discards information. The continuous total score was used as the dependent variable in the regression model.

2.6 Statistical Analysis

Categorical variables were presented as frequencies and percentages and were compared using Fisher's exact test or chi-square test, as appropriate. Continuous and ordinal variables, including postoperative NRS scores, opioid requirements, and SII values, were analyzed using the Mann–Whitney U test when appropriate. Postoperative QoR-15 was also analyzed categorically using the chi-square test. Between-group differences are presented with 95% confidence intervals (CI) for cortisol and SII. Because p-values for continuous outcomes were derived from the Mann–Whitney U test, these parametric intervals are descriptive approximations and should be read together with the rank-based tests. Secondary outcomes were not adjusted for multiple comparisons and are considered exploratory. All randomized participants were analyzed in their allocated groups; no outcome data were missing, so no imputation was required (complete-case analysis). Multivariable linear regression (ordinary least squares, all variables entered simultaneously) was used to examine the association of the 24-hour QoR-15 total score (continuous dependent variable) with three explanatory variables: 24-hour serum cortisol (μg/dL), 24-hour SII (per unit), and postoperative NRS score (0–10, continuous). Coefficients are reported as unstandardized B with standard error, 95% CI, standardized β, and p-value. Statistical significance was distinguished from clinical importance by considering the magnitude of effects relative to the 8-point QoR-15 difference used in the sample size calculation. Statistical analyses were performed using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA). A two-sided p-value of <0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Characteristics of Participants

A total of 38 patients undergoing major abdominal gynecologic surgery were included and analyzed, with 19 patients allocated to each group. All participants fulfilled the predefined eligibility criteria. No clinically relevant differences were observed in baseline or perioperative characteristics between groups. The mean age was 45.16 ± 12.88 years in the ESP + dexmedetomidine group and 43.21 ± 12.07 years in the ESP group (p = 0.633). Mean operative duration was 134.21 ± 25.24 and 138.95 ± 26.85 minutes (p = 0.545), while mean intraoperative blood loss was 410.53 ± 80.93 and 384.21 ± 60.21 mL, respectively (p = 0.316). No participants were withdrawn or lost to follow-up, and no data were missing for the analyzed outcomes (Table 1).

Table 1. Baseline and perioperative characteristics of study participants

Characteristic	ESP + Dexmedetomidine (n = 19)	ESP (n = 19)	*p* value
Age (years), mean ± SD	45.16 ± 12.88	43.21 ± 12.07	0.633[a]
Operative duration (minutes), mean ± SD	134.21 ± 25.24	138.95 ± 26.85	0.545[c]
Intraoperative blood loss (mL), mean ± SD	410.53 ± 80.93	384.21 ± 60.21	0.316[c]

Data are presented as mean ± standard deviation (SD) or number (percentage). [a]Unpaired t-test; [b]Fisher's exact test; [c]Mann–Whitney U test.

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3.2 Postoperative Pain and Opioid Requirement

Preoperatively, NRS categories were comparable between groups (p = 0.319). At 12 hours postoperatively, the ESP + dexmedetomidine group had a significantly more favorable NRS distribution, with 10 patients (52.6%) categorized as having low pain and 9 (47.4%) moderate pain, compared with 5 (26.3%), 9 (47.4%), and 5 (26.3%) patients with low, moderate, and high pain, respectively, in the ESP group (p = 0.043). At 24 hours, all 19 patients (100%) in the ESP + dexmedetomidine group had low NRS scores, compared with 6 (31.6%) in the ESP group, in which 4 (21.1%) had moderate and 9 (47.4%) had high pain scores (p < 0.001). Postoperative opioid requirements were also significantly lower in the ESP + dexmedetomidine group than in the ESP group (0.00 ± 0.00 vs. 17.10 ± 16.78 μg, respectively; p < 0.001). The mean difference in rescue fentanyl consumption was −17.1 μg (95% CI −25.2 to −9.0); the standard deviation in the ESP group (16.78 μg) was nearly equal to its mean, indicating a skewed distribution, and no rescue opioid was required in the dexmedetomidine group (Table 2).

Table 2. Comparison of postoperative NRS scores and additional opioid requirements between groups

Variable	ESP + Dexmedetomidine (n = 19)	ESP (n = 19)	95% CI	*p* value
Preoperative NRS, n (%)				0.319[a]
Low	0 (0.0)	0 (0.0)		
Moderate	13 (68.4)	10 (52.6)		
High	6 (31.6)	9 (47.4)		
NRS at 12 hours postoperative, n (%)				0.043[b]*
Low	10 (52.6)	5 (26.3)		
Moderate	9 (47.4)	9 (47.4)		
High	0 (0.0)	5 (26.3)		
NRS at 24 hours postoperative, n (%)				<0.001[b]*
Low	19 (100.0)	6 (31.6)		
Moderate	0 (0.0)	4 (21.1)		
High	0 (0.0)	9 (47.4)		
Additional opioid requirement, mean ± SD, μg	0.00 ± 0.00	17.10 ± 16.78	−25.2 – −9.0	<0.001[c]*

Data are presented as numbers (percentages) or mean ± standard deviation (SD). [a]Fisher's exact test; [b]Mann–Whitney U test; [c]Mann–Whitney U test. *Statistically significant at p < 0.05. NRS categories: low 0–3, moderate 4–6, high 7–10.

3.3 Cortisol and Systemic Immune-Inflammation Index

Preoperative cortisol concentrations did not differ significantly between groups (108.91 ± 50.18 vs. 129.96 ± 57.01 μg/dL; p = 0.255). Postoperatively, cortisol concentrations were significantly lower in the ESP + dexmedetomidine group at both 12 hours (83.97 ± 84.69 vs. 138.11 ± 59.28 μg/dL; p = 0.002) and 24 hours (43.16 ± 26.44 vs. 110.44 ± 60.47 μg/dL; p < 0.001) (Table 3). Similarly, preoperative SII values were comparable between groups (1,517.49 ± 887.66 vs. 1,801.11 ± 1,289.41; p = 0.693). At 12 hours postoperatively, SII was significantly lower in the ESP + dexmedetomidine group (1,166.99 ± 842.38 vs. 2,183.72 ± 1,701.60; p = 0.032), and this difference remained significant at 24 hours (1,200.45 ± 695.78 vs. 2,495.09 ± 2,128.16; p = 0.030) (Table 4). Mean differences (ESP + dexmedetomidine minus ESP) for cortisol were −21.1 μg/dL preoperatively (95% CI −56.4 to 14.3), −54.1 μg/dL at 12 hours (95% CI −102.4 to −5.9), and −67.3 μg/dL at 24 hours (95% CI −98.5 to

−36.1). For SII, the corresponding differences were −283.6 (95% CI −1,015.2 to 448.0), −1,016.7 (95% CI −1,911.6 to −121.9), and −1,294.6 (95% CI −2,360.5 to −228.8). Several intervals are wide and approach zero at their upper bounds, and the 12-hour cortisol standard deviation in the dexmedetomidine group exceeded its mean, so the magnitude of these differences is estimated with limited precision.

Table 3. Comparison of cortisol levels between study groups

Cortisol level (mean ± SD, µg/dL)	ESP + Dexmedetomidine (n = 19)	ESP (n = 19)	95% CI	*p* value
Preoperative	108.91 ± 50.18	129.96 ± 57.01	−56.4 − 14.3	0.255
12 hours postoperative	83.97 ± 84.69	138.11 ± 59.28	−102.4 − −5.8	0.002*
24 hours postoperative	43.16 ± 26.44	110.44 ± 60.47	−98.5 − −36.1	<0.001*

Data are presented as mean ± SD. All comparisons were performed using the Mann–Whitney U test. *Statistically significant at $p < 0.05$.

Table 4. Comparison of Systemic Immune-Inflammation Index between study groups

SII (mean ± SD)	ESP + Dexmedetomidine (n = 19)	ESP (n = 19)	95% CI	*p* value
Preoperative	1,517.49 ± 887.66	1,801.11 ± 1,289.41	−1,015.2 − 448.0	0.693
12 hours postoperative	1,166.99 ± 842.38	2,183.72 ± 1,701.60	−1,911.6 − −121.9	0.032*
24 hours postoperative	1,200.45 ± 695.78	2,495.09 ± 2,128.16	−2,360.5 to −228.8	0.030*

Data are presented as mean ± SD. Comparisons were performed using the Mann–Whitney U test. *Statistically significant at $p < 0.05$.

3.4 Quality of Recovery

Preoperative QoR-15 categories were comparable between groups (p = 1.000). Postoperatively, good recovery was observed in 11 patients (57.9%) in the ESP + dexmedetomidine group compared with 2 patients (10.5%) in the ESP group, whereas poor recovery was observed in 8 (42.1%) and 17 (89.5%) patients, respectively ($p < 0.001$). The risk difference for good recovery was 47.4 percentage points (95% CI 17.3 to 67.8); this estimate rests on 13 patients with good recovery in total (11 and 2) and is therefore imprecise (**Figure 1**).

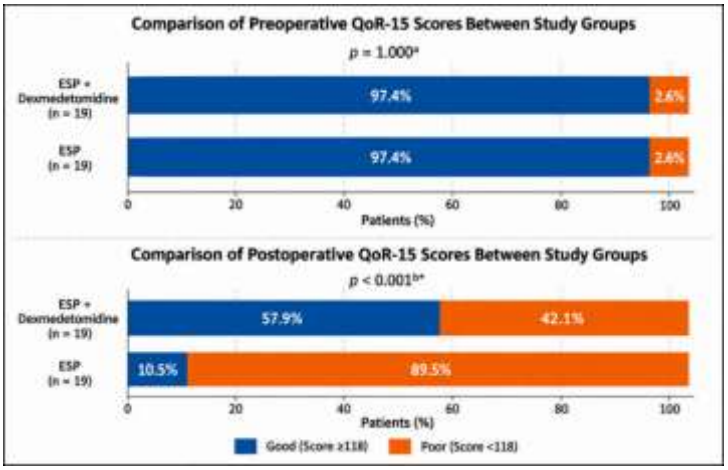


Figure 1. Comparison of Quality of Recovery Levels Between Study Groups.

[a] Fisher's exact test; [b] Chi-square test. *Statistically significant at $p < 0.05$.

3.5 Multivariate Analysis

In linear regression, postoperative cortisol and NRS were independently associated with QoR-15. Each 1 μg/dL increase in 24-hour postoperative cortisol was associated with a 0.108-point decrease in QoR-15 (B = −0.108, β = −0.493, p = 0.002), while each one-point increase in postoperative NRS was associated with a 2.227-point decrease in QoR-15 (B = −2.227, β = −0.394, p = 0.028). In contrast, 24-hour postoperative SII was not independently associated with QoR-15 (B = 0.000, β = 0.054, p = 0.777) (Table 5). The 95% CIs were −0.173 to −0.043 for the cortisol coefficient and −4.198 to −0.256 for the NRS coefficient, the latter approaching zero at its upper bound; the SII coefficient was essentially zero. These coefficients describe cross-sectional associations measured at the same time in the pooled sample, so they cannot establish temporal order or causality, and cortisol and pain may be correlated with each other.

Table 5. Multivariable Analysis of Factors Associated with QoR-15

Independent variable	B	SE	Standardized β	*p* value	95% CI
Constant	124.981	3.319	–	<0.001	
Cortisol at 24 hours postoperative	−0.108	0.032	−0.493	0.002*	−0.173 − −0.043
SII at 24 hours postoperative	0.000	0.001	0.054	0.777	−0.173 − 0.003
Postoperative NRS score	−2.227	0.970	−0.394	0.028*	−4.198 − −0.256

B, regression coefficient; SE, standard error; β, standardized regression coefficient. *Statistically significant at p < 0.05

3.6 Discussion

The principal finding of this randomized controlled trial was that adding dexmedetomidine to levobupivacaine in ESP block was associated with better early postoperative analgesia, lower rescue opioid requirements, lower postoperative cortisol concentrations and SII, and a more favorable distribution of QoR-15 recovery categories in patients undergoing major abdominal gynecologic surgery. Although the analgesic and opioid-sparing effects of dexmedetomidine are consistent with previous studies of ESP block in other surgical populations, the present findings provide additional clinical observations regarding perioperative stress-related biomarkers and early patient-reported recovery in this specific population. Importantly, the exploratory multivariable analysis showed that postoperative cortisol and pain intensity were independently associated with QoR-15, whereas SII was not. This distinction suggests that the observed reduction in systemic inflammatory status should not automatically be interpreted as an independent determinant of early recovery. Rather than establishing a novel molecular mechanism, the study contributes preliminary clinical evidence concerning the different relationships of neuroendocrine stress, systemic inflammation, and pain with postoperative recovery. These results come from a small trial (38 patients, 19 per group) with 24-hour follow-up and are subject to the limited precision indicated by several wide confidence intervals; they should be interpreted in proportion to this evidence, as preliminary and hypothesis-generating rather than confirmatory.

The findings are compatible with the view that dexmedetomidine may be a useful adjuvant to local anesthetic in ESP block, although this small trial was not designed to confirm that conclusion. Its analgesic effect is thought to be mediated through a combination of peripheral and central mechanisms. Activation of α2-adrenergic receptors reduces norepinephrine release and enhances descending inhibitory pain pathways, while effects on neural membrane ion currents may prolong the duration of sensory blockade. In addition, local vasoconstrictive effects may slow systemic absorption of the local anesthetic and prolong its action. These mechanisms, which were not measured in the present study, offer a plausible but untested explanation for the superior postoperative analgesia observed with the combination of dexmedetomidine and levobupivacaine. The present findings are consistent with randomized clinical evidence from thoracic surgery, in which dexmedetomidine added to ropivacaine in ESP block reduced postoperative pain, prolonged sensory blockade, delayed the first requirement for patient-controlled analgesia, and reduced rescue analgesic use.(Gao et al., 2019) Similar findings have been reported in patients undergoing laparoscopic sleeve gastrectomy, in whom 0.5 or 1 μg/kg dexmedetomidine prolonged the time to first analgesic administration and reduced postoperative opioid and ketorolac consumption.(Abdel et al., 2024)

The consistency of these observations with the broader evidence base is further supported by the meta-analysis of Li et al. (2024), which demonstrated that dexmedetomidine added to local anesthetic in ESP block reduced pain intensity at rest and during movement, prolonged sensory block duration, delayed the need for rescue analgesia, and reduced morphine consumption. Importantly, the dose used in the present study was 0.5 μg/kg, which falls within the dose range evaluated in this meta-analysis.(Li et al., 2024) Thus, the analgesic benefit observed in the present study is biologically plausible and in line with

prior evidence, although the precision of the present estimates is limited. Nevertheless, dexmedetomidine remains associated with potential adverse effects, particularly bradycardia, hypotension, and sedation, emphasizing the importance of perioperative hemodynamic surveillance when it is used as a regional anesthetic adjuvant.(Wu et al., 2020; Li et al., 2024)

The reduction in postoperative opioid requirements has important clinical implications. Opioid-sparing analgesia is a major component of contemporary perioperative care because excessive opioid exposure may contribute to nausea and vomiting, sedation, impaired gastrointestinal function, and delayed functional recovery. A prolonged analgesic effect of dexmedetomidine may therefore explain the lower need for rescue opioid administration, although block duration was not directly assessed here. Moreover, because rescue fentanyl was triggered by the NRS score, pain scores and opioid consumption are not independent outcomes, and the absence of any rescue opioid in the dexmedetomidine group) against a skewed distribution in the ESP group limits the precision of the mean difference. In addition to direct analgesic effects, dexmedetomidine may attenuate nociceptive amplification through suppression of sympathetic activity and proinflammatory signaling. Previous evidence has demonstrated reductions in proinflammatory cytokines such as TNF-α and IL-6 following dexmedetomidine administration, which raises a possible, but here untested, interaction between analgesic and anti-inflammatory mechanisms.(Abu El Hassan et al., 2024; Li et al., 2024; Barakat et al., 2025)

Postoperative cortisol concentrations were lower in the ESP–dexmedetomidine group than in the ESP-only group at both 12 and 24 hours. These findings are consistent with a difference in the postoperative neuroendocrine stress response between the treatment groups. Cortisol is influenced by several factors, including surgical tissue injury, circadian variation, psychological stress, anesthetic and analgesic medications, and the timing of blood sampling. Therefore, the observed between-group differences cannot be attributed exclusively to direct suppression of the hypothalamic–pituitary–adrenal axis by dexmedetomidine.(Wang et al., 2019; Wu et al., 2020; Ivascu et al., 2024; Acharya et al., 2025) Moreover, the present study did not measure catecholamines, adrenocorticotropic hormone, or other pathway-specific markers. The results should consequently be interpreted as evidence of lower postoperative cortisol concentrations associated with the intervention, rather than proof of a specific neuroendocrine mechanism. Lower cortisol in the dexmedetomidine group may also partly reflect better pain control and reduced opioid exposure rather than a direct effect of the drug on the stress axis, and this study cannot distinguish between these possibilities. The observed reductions in cortisol and SII are therefore differences in biomarker values, not evidence of a demonstrated mechanism of improved recovery, and the intervals around the cortisol differences are wide. The independent association between 24-hour cortisol and QoR-15 further identifies cortisol as a potentially relevant correlate of early recovery, although the observational nature of this association does not establish causality.

The lower SII in the dexmedetomidine group is of interest, but as a composite of blood-cell counts it cannot by itself indicate that the effects of dexmedetomidine extend beyond neural modulation. SII integrates neutrophil, platelet, and lymphocyte counts and therefore provides a composite representation of systemic inflammatory and immune responses (Cheng et al., 2026). SII was lower in the ESP–dexmedetomidine group at 12 and 24 hours after surgery, indicating a difference in the postoperative profile of circulating inflammatory and immune cell counts between the groups. Nevertheless, SII is a composite index derived from platelet, neutrophil, and lymphocyte counts and does not directly measure cytokine activity or a specific molecular inflammatory pathway. The observed differences therefore support an association between the intervention and postoperative systemic inflammatory status, but they do not establish direct immunomodulation or identify the biological pathway responsible for the changes. This distinction is important because experimental and clinical studies investigating dexmedetomidine-mediated inflammatory signaling cannot be directly extrapolated to the present study without pathway-specific measurements.

This result is consistent with previous evidence that dexmedetomidine can attenuate perioperative inflammation. Wang et al. (2019), in a meta-analysis involving 67 studies and 4,842 surgical patients, reported reductions in several inflammatory and stress-related markers, including IL-6, TNF-α, and C-reactive protein, together with increased IL-10 and preservation of cellular immune function. Although SII was not directly evaluated in that meta-analysis, its constituent cellular components are affected by inflammatory and immune modulation.(Wang et al., 2019) The findings are also compatible with observations from Chen et al., who reported reduced postoperative changes in the neutrophil-to-lymphocyte ratio following intraoperative dexmedetomidine in patients undergoing laparoscopic pancreaticoduodenectomy (Chen et al., 2023).

Notably, postoperative SII was not independently associated with QoR-15 in the multivariable analysis, whereas cortisol and pain intensity were. This finding suggests that the difference in systemic inflammatory status between groups did not translate into a demonstrable independent association with early patient-reported recovery in the present sample. However, the

nonsignificant regression coefficient should not be interpreted as evidence that inflammation has no role in postoperative recovery. The sample size, short observation period, variability in SII, and potential overlap between clinical and biological responses may have limited the ability to detect such an association. Larger studies incorporating repeated biomarker measurements and adequately powered analyses are required to clarify whether changes in systemic inflammatory markers provide information about recovery beyond that captured by pain intensity and neuroendocrine stress markers.

An additional observation is that the difference between groups was also reflected in patient-reported recovery categories. The higher proportion of patients with good recovery in the dexmedetomidine group suggests a possible improvement in early recovery that extends beyond pain intensity alone. However, whether this difference is clinically important cannot be concluded from the present data: continuous QoR-15 scores were not evaluated against a minimal clinically important difference, the ≥118 cutoff is study-specific, the categorical estimate rests on 13 patients with good recovery (risk difference 47.4 percentage points, 95% CI 17.3 to 67.8), and recovery was assessed only at 24 hours. No inference can be drawn about long-term recovery, length of stay, complications, or other surgical outcomes beyond this follow-up period. Previous studies using ESP block have similarly reported improved QoR-15 following the addition of dexmedetomidine. Guo et al. found higher 24-hour QoR-15 scores with dexmedetomidine added to ropivacaine (Guo et al., 2023), while Yi-han et al. reported improved QoR-15 during the first and second postoperative days following ESP block with dexmedetomidine (Yi-han et al., 2022).

The relationship between cortisol, postoperative pain, and QoR-15 is compatible with the view that postoperative recovery is related to both nociceptive and stress responses. Cortisol had the largest standardized coefficient in the multivariable model ($\beta = -0.493$ versus -0.394 for NRS), although the difference is small and the estimates are imprecise with 38 observations, so relative importance cannot be ranked reliably; this is consistent with its role as an integrated marker of the neuroendocrine response to surgical trauma. Activation of the HPA axis is not driven exclusively by pain but also by tissue injury, inflammation, sympathetic activation, sleep disturbance, anxiety, and metabolic changes (Knezevic et al., 2023; Acharya et al., 2025). Consequently, cortisol may capture a broader physiological burden than pain intensity alone. Statistical significance of these coefficients should not be equated with clinical importance: a 10 μg/dL difference in 24-hour cortisol corresponds to about 1.1 QoR-15 points, much smaller than the 8-point difference assumed in the sample size calculation, whereas each 1-point increase in NRS corresponds to about 2.2 points. These coefficients describe associations at a single time point in pooled data and do not show that lowering cortisol or pain would improve recovery.

Postoperative NRS also remained independently associated with QoR-15. This finding is biologically plausible because uncontrolled pain can perpetuate peripheral and central sensitization and interfere directly with mobilization, sleep, emotional well-being, and physical independence. Neurotransmitters such as glutamate, substance P, and calcitonin gene-related peptide contribute to the maintenance of nociceptive signaling and central sensitization.(Iyengar *et al.*, 2017; Karcz *et al.*, 2024). Thus, the independent contribution of pain to QoR-15 emphasizes that effective postoperative recovery requires adequate analgesia in addition to attenuation of systemic stress.

In contrast, SII was not independently associated with QoR-15 after adjustment for cortisol and NRS. This finding does not necessarily contradict the between-group reduction in SII. Rather, one speculative explanation is that systemic inflammation affects perceived recovery indirectly through pain, neuroendocrine stress, and other pathways. Because SII is derived from circulating neutrophil, platelet, and lymphocyte counts, it represents systemic inflammatory status but does not directly measure functional recovery or patient experience. The absence of an independent association with QoR-15 therefore suggests that SII may be more useful as a biological marker of the systemic response to surgery than as a direct surrogate for patient-centered recovery.

The temporal relationship between cortisol and pain also warrants consideration. In exploratory analyses, the association between cortisol and NRS appeared at 24 hours but not at baseline or 12 hours. Cortisol is a dynamic biomarker influenced by sampling time, circadian variation, biological variability, anxiety, inflammation, and perioperative medications. Consequently, a single cortisol measurement may not directly represent pain intensity at every postoperative time point.(Villafañe et al., 2020) The absence of a significant association at 12 hours may therefore reflect the complex and evolving HPA response during the early postoperative period. Importantly, the observed association at 24 hours should be interpreted as a relationship between two components of the postoperative stress response rather than evidence that cortisol directly causes pain. Similar evidence indicates that the relationship between cortisol and pain may vary according to postoperative phase and patient characteristics.(Villafañe et al., 2020)

Several limitations should be considered. This was a small (n = 38), single-center trial, which limits statistical precision and generalizability: several confidence intervals are wide, the sample was restricted to ASA I–II patients aged 18–60 years, and with simple randomization a chance imbalance in unmeasured prognostic factors cannot be excluded (baseline cortisol and SII were numerically lower in the dexmedetomidine group, although not significantly so). Only QoR-15 was used for the sample size calculation, and the pain, opioid, cortisol, and SII analyses were exploratory and not adjusted for multiple comparisons, so p values close to 0.05 (e.g., NRS at 12 hours, SII) should be interpreted cautiously. The 24-hour follow-up precludes assessment of longer-term pain, opioid use, quality of life, and recovery; the results should therefore not be taken to indicate long-term benefit or improved surgical outcomes. The study was single-blind: although participants and outcome assessors were blinded, the anesthesiologist performing the ESP block was not, introducing potential performance bias, which is relevant because pain scores and QoR-15 are subjective and rescue analgesia was triggered by NRS scores. Pain scores and opioid consumption were also interdependent because of protocol-driven rescue fentanyl. In addition, cortisol and SII are indirect biomarkers and do not definitively reflect specific inflammatory or neuroendocrine pathways. Biomarkers were measured at only three time points and may have been affected by diurnal variation; QoR-15 was analyzed mainly as a dichotomous outcome with a study-specific cutoff; the regression model included three predictors in 38 observations and was cross-sectional at 24 hours; and adverse-event data were limited (see above). Larger multicenter studies with longer follow-up and more comprehensive biomarker assessment are warranted. Future larger trials should include more heterogeneous populations, longer follow-up (days to weeks) with standardized recovery assessments (continuous QoR-15 scores at multiple time points interpreted against a minimal clinically important difference, mobilization, return of bowel function, and length of stay), prespecified safety outcomes, and specific biomarkers such as IL-6, TNF-α, IL-10, and C-reactive protein. Further evaluation of the optimal dexmedetomidine dose, concentration, and administration route is also needed to determine whether its analgesic, stress-modulating, and immunomodulatory effects translate into sustained clinical benefits.

4. CONCLUSION

Adding dexmedetomidine to levobupivacaine in ESP block was associated with better postoperative pain control, lower rescue opioid requirements, lower postoperative cortisol and SII values, and a more favorable distribution of early QoR-15 recovery categories in patients undergoing major abdominal gynecologic surgery. Postoperative cortisol and pain intensity were independently associated with QoR-15, whereas SII was not independently associated with recovery in the fitted model. These findings provide preliminary clinical evidence concerning the relationships between perioperative stress-related markers and early postoperative recovery. However, the observed reductions in cortisol and SII do not demonstrate a mechanism of improved recovery, the study does not establish a causal relationship between biomarker changes and recovery, and, given the small sample, 24-hour follow-up, and single-blind design, the results do not show long-term benefit or improved surgical outcomes. Larger, adequately powered studies with longer follow-up and more comprehensive biological assessments are warranted to validate these observations, to assess safety, and to determine their clinical importance.

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AUTHOR CONTRIBUTIONS

Bara Adithya: Conceptualization, Study Design, Writing—Original Draft, Figure Design.

Andi Muhammad Takdir Musba: Conceptualization, Study Design, Interpretation of Results, Writing—Review & Editing.

Madonna Damayanthie Datu: Investigation, Data Collection.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

This study was conducted in accordance with the ethical principles for research involving human participants. The study protocol was approved by the Health Research Ethics Committee of Universitas Hasanuddin/Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia (Ethics Approval No. 863/UN4.6.4.5.31/PP36/2026; approved on 14 July 2026). Written informed consent was obtained from all participants before enrollment.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request and with the corresponding author's permission.

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