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ORIGINAL ARTICLE

Effect of Transversus Abdominis Plane Block with Dexmedetomidine and Clonidine on Numerical Rating Scale and Interleukin–6

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Abstract

Background: The use of adjuvants like dexmedetomidine and clonidine in Tranversus Abdominis Plane (TAP) blocks can enhance analgesic effects. This study aimed to compare the impact of these adjuvants on TAP blocks by measuring postoperative pain using the numerical rating scale (NRS) and interleukin-6 (IL-6) levels.

Method: This study was conducted from January to April 2024 at the Central Surgical Installation of Dr. Moewardi using a double-masked randomized controlled trial design. The study involved 30 patients undergoing cesarean section, divided into two groups: Group A (15 received a TAP block with dexmedetomidine 0.5 mcg/kgBB) and Group B (15 received a TAP block with clonidine 0.5 mcg/kgBB).

Results: Independent tests revealed significant differences in NRS and IL-6 levels between the groups ($p < 0.001$), indicating that dexmedetomidine is superior at preventing NRS and IL-6 elevation.

Discussion: Conventional epidural opioids effectively manage pain but cause significant side effects and serious risks, including delayed respiratory depression in mothers and adverse effects on breastfed infants, necessitating alternative approaches. TAP block with dexmedetomidine and clonidine adjuvants demonstrated significant effectiveness in reducing postoperative pain, with dexmedetomidine proving superior in prolonging analgesia duration, decreasing rescue medication requirements, and reducing opioid consumption through its anti-inflammatory effects.

Conclusion: These findings highlight the positive effects of dexmedetomidine in reducing postoperative inflammation and pain. The results provide grounds for considering dexmedetomidine as an adjuvant in TAP blocks to enhance effective postoperative pain management.

Keywords: Clonidine; dexmedetomidine; interleukin-6; transversus abdominis plane block; postoperative pain

Introduction

Postoperative pain is a common problem experienced by more than 80% of surgical patients, with approximately 75% reporting moderate to extreme pain.[1,2] Data from Ethiopia indicate that the prevalence of moderate to severe pain reaches 85.5% in post-cesarean section patients,[3]. At the same time, studies in Indonesia show that 30%–55% of abdominal surgery patients experience moderate to severe pain during the first 24–48 hours postoperatively.[4,5] In Indonesia, the prevalence of acute postoperative pain varies across

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institutions, with incidence rates remaining concerning despite the availability of various analgesic modalities.[5]

The management of this pain was previously dominated by opioid use, but increasing morbidity and mortality associated with opioid side effects have driven the development of safer and more effective pain treatment strategies.[2,6] Although effective in managing pain, this approach often causes side effects such as nausea, vomiting, pruritus, constipation, urinary retention, and excessive sedation.[7] In obstetric populations, opioid use carries additional specific risks. Hydrophilic opioids such as morphine can cause delayed respiratory depression in mothers. In contrast, lipophilic opioids such as pethidine are excreted in breast milk and can cause neonatal sedation, feeding difficulties, and respiratory depression in infants.[7] The FDA and American Academy of Pediatrics warn that up to 28% of women are ultra-rapid CYP2D6 metabolizers who rapidly convert codeine and tramadol to morphine, resulting in high morphine levels in breast milk that are dangerous to infants.[7] Logistical challenges and medical contraindications also limit neuraxial opioid use.

Regional anesthesia, such as TAP block, has become a popular choice in postoperative pain management because it can reduce acute pain, nausea, vomiting, and pulmonary complications, and has additional benefits such as decreased cancer recurrence and surgical site infection.[8] TAP blocks spinal nerves from T7 to L1, providing effective analgesia for various abdominal surgeries.[9] This technique involves the injection of local anesthetic into the fascial plane between the internal oblique muscle and transversus abdominis muscle using local anesthetic bupivacaine 0.2% 20 mL on each side with the help of ultrasonographic guidance.[10] Compared to local anesthetic infiltration at the surgical wound, TAP block significantly reduces pain scores and opioid consumption after abdominal surgery.[10] Meta-analysis data show that TAP block can reduce the incidence of postoperative nausea, reduce required doses of fentanyl and morphine, decrease Visual Analogue Scale (VAS) scores, and reduce extubation time.[11] In the context of cesarean section, a meta-analysis of 20 randomized controlled trials shows that TAP block provides superior analgesia when long-acting intrathecal opioids are not used.[12]

One of the main limitations of the TAP block is its limited duration of effect, restricted to the duration of action of the local anesthetic administered. To address this, the use of adjuvants such as dexmedetomidine and clonidine in TAP blocks can prolong analgesia. Studies show that adding dexmedetomidine or clonidine to bupivacaine prolongs analgesic duration and reduces postoperative analgesic requirements.[13,14] Both drugs are α2-adrenergic agonists that work through central and peripheral mechanisms. Centrally, activation of α2A receptors in the locus coeruleus inhibits adenylyl cyclase and causes hyperpolarization of noradrenergic neurons, producing hypnotic, sedative, and analgesic effects.[15] At the spinal level, stimulation of α2 receptors in the dorsal horn of the spinal cord inhibits nociceptive neurons and reduces substance P release.[15]

The main advantage of dexmedetomidine is its higher selectivity for α2A receptors compared to clonidine.[16] Systematic meta-analyses show that dexmedetomidine as an adjuvant to local anesthetics in TAP block significantly reduces postoperative pain intensity and reduces opioid consumption, with significant prolongation of block duration.[17] Studies show that adding dexmedetomidine 0.5 μg/kg as an adjuvant to 0.25% ropivacaine in TAP block significantly prolongs postoperative analgesia duration with lower pain scores and reduced analgesic consumption during 24 hours postoperatively, without significant side effects.

Clonidine, as an α2-adrenergic agonist, has also been investigated as a local anesthetic adjuvant in TAP block. Studies in cesarean section show that adding clonidine 1 μg/kg to 0.25% levobupivacaine 20 mL in bilateral TAP block significantly increases postoperative analgesia duration, reduces rescue analgesic requirements, and increases maternal comfort.[18] Clonidine may be more preferred, especially in developing countries, due to its easier availability and lower cost compared to dexmedetomidine. [19]

Interleukin-6 (IL-6) is a pro-inflammatory cytokine released in response to tissue injury and plays an important role in the postoperative physiological response.[20] Postoperative IL-6 elevation proportional to the magnitude of surgical stress has been well documented, with peaks occurring at 24 hours postoperatively.[20,21] IL-6 levels >130 pg/mL measured 24 hours postoperatively are predictive of postoperative complications.[21]

Dexmedetomidine has been shown to have significant anti-inflammatory effects by modulating cytokine release and immune cell activity. Studies show that dexmedetomidine inhibits the intraoperative stress response, as demonstrated by decreased plasma levels of norepinephrine, epinephrine, cortisol, TNF-α, and IL-6.[22]

Although evidence shows that both dexmedetomidine and clonidine are effective as TAP block adjuvants, direct comparative studies in obstetric populations undergoing cesarean section remain limited. Furthermore, data on the anti-inflammatory effects of both adjuvants, as measured by objective markers such as IL-6, remain limited. This study aimed to compare the impact of these two adjuvants on the TAP block by measuring postoperative pain using the numerical rating scale (NRS) and interleukin-6 (IL-6) levels, providing a comprehensive perspective on their effectiveness in postoperative pain management and the inflammatory response.

Subjects and Methods

This study employed a double-masked, randomized controlled trial (RCT) design with random allocation, and both investigators and patients were blinded to treatment assignment. The study was conducted in the Central Surgical Installation at Dr. Moewardi General Hospital, Central Java Province, from January to April 2024. This study received approval from the Health Research Ethics Committee of Dr. Moewardi General Hospital with approval letter number 310/H/HREC/2024.

The study population consisted of patients undergoing cesarean section with subarachnoid block regional anesthesia technique who subsequently received postoperative analgesia with TAP block method and dexmedetomidine or clonidine adjuvant at Dr. Moewardi General Hospital from January to April 2024. Inclusion criteria included age 20–40 years, undergoing a cesarean section procedure with subarachnoid block anesthesia, physical status ASA II or II-E, ability to understand and provide pain assessment based on NRS, and willingness to sign informed consent.

On the other hand, patients with a history of cardiac disease, respiratory disease, kidney or liver disease, blood coagulation disorders, local site infection, allergy to anesthetic drugs, history of drug abuse, history of psychological illness, and patients who refused were not included in the study. Circumstances such as changes in anesthesia type by the operator during surgery, side effects such as allergy or hemodynamic instability during observation, patients or families withdrawing during the study, or side effects/death/loss to follow-up were excluded from analysis (drop out).

Samples were randomly taken from the population meeting the inclusion and exclusion criteria. Using the sample calculation formula for two-sample hypothesis testing, the result was n=15 per group. The minimum total sample size was 30 participants, with each group consisting of 15. Samples were allocated to treatment groups randomly using a random number generator. All study participants provided written informed consent before participating in this study. The research workflow and procedure are shown in Figure 1.

Under aseptic precautions, spinal anesthesia was administered with the patient in a sitting position. A 25–27 gauge spinal needle was used to inject 15 mg of hyperbaric levobupivacaine into the L3–L4 or L4–L5 intervertebral space. The TAP block

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was performed bilaterally under ultrasound guidance after completion of the cesarean section, with the patient in the supine position. This fascial plane block targets the spinal nerves from T7 to L1 that course within the plane between the internal oblique and transversus abdominis muscles. A high-frequency linear ultrasound probe (10–13 MHz) was placed transversely along the mid-axillary line between the costal margin and the iliac crest.

After the fascial plane was clearly visualized, a block needle was inserted using an in-plane technique from posterior to anterior, parallel to the ultrasound beam, allowing continuous real-time visualization of the needle tip throughout needle advancement. In the setting of cesarean section, the lateral approach is preferred because it adequately covers the dermatomes relevant to a Pfannenstiel incision in the lower abdomen.

The local anesthetic used in this study was 0.25% bupivacaine, a long-acting amide local anesthetic widely used as a standard agent for TAP blocks in clinical studies. The 0.25% concentration was chosen to provide an optimal balance between analgesic efficacy and safety, with a low risk of systemic toxicity at recommended doses. In group A, 20 mL of 0.25% bupivacaine was combined with 0.5 μg/kg dexmedetomidine (diluted in 2 mL of 0.9% normal saline), resulting in a total volume of 22 mL per side. In group B, 20 mL of 0.25% bupivacaine was combined with clonidine 0.5 μg/kg (diluted in 2 mL of 0.9% normal saline), resulting in a total volume of 22 mL per side.

The total bupivacaine dose administered bilaterally remained within the recommended maximum dose for regional infiltration, up to about 2 mg/kg without epinephrine. Peripheral venous blood samples for serum IL-6 measurement were obtained at two time points:
A preoperative sample taken before spinal anesthesia as the baseline value.
A postoperative sample drawn 12 hours after surgery.

The 12-hour time point was chosen based on published evidence indicating that serum IL-6 levels reach peak or near-peak concentrations within 6–24 hours after surgical trauma, so measurement at 12 hours captures the inflammatory response at a clinically relevant phase close to the expected maximum. Serum IL-6 concentrations were determined using an enzyme-linked immunosorbent assay (ELISA) and expressed in pg/mL. Postoperative pain was assessed using the Numerical Rating Scale (NRS 0−10). The observer recorded the time elapsed until the patient requested rescue analgesia, which was administered as 30 mg of intravenous (IV) ketorolac.

Statistical analysis was performed using IBM SPSS Statistics 26. Data normality test using the Shapiro-Wilk test. Homogeneity test using the Levene test. Normally distributed numerical data were presented as mean (standard deviation) and analyzed with independent t-tests and paired t-tests for pre-post comparisons. Non-normally distributed data were analyzed using the Mann-Whitney and Wilcoxon tests. The significance level was set at $p<0.05$ with a 95% confidence interval.

Results

This study consisted of 30 patients undergoing cesarean section, divided into two groups: Group A (15 patients received a TAP block with dexmedetomidine adjuvant 0.5 mcg/kg) and Group B (15 patients received a TAP block with clonidine adjuvant 0.5 mcg/kg). The baseline characteristics of the study subjects are shown in Table 1.

The mean patient age was 31.57±4.11 years, with Group A at 32.00±4.69 years and Group B at 31.13±3.54 years. Statistical test results showed no significant difference in age between the two groups (p=0.573), indicating homogeneous patient age in this study. The mean patient BMI was 28.43±2.86, with mean BMIs of 28.07±1.98 for Group A and 28.80±3.75 for Group B. Statistical tests showed no significant difference in BMI between the two groups (p=0.850), indicating homogeneous patient BMIs in this study.

Differences in NRS are shown in Table 2.

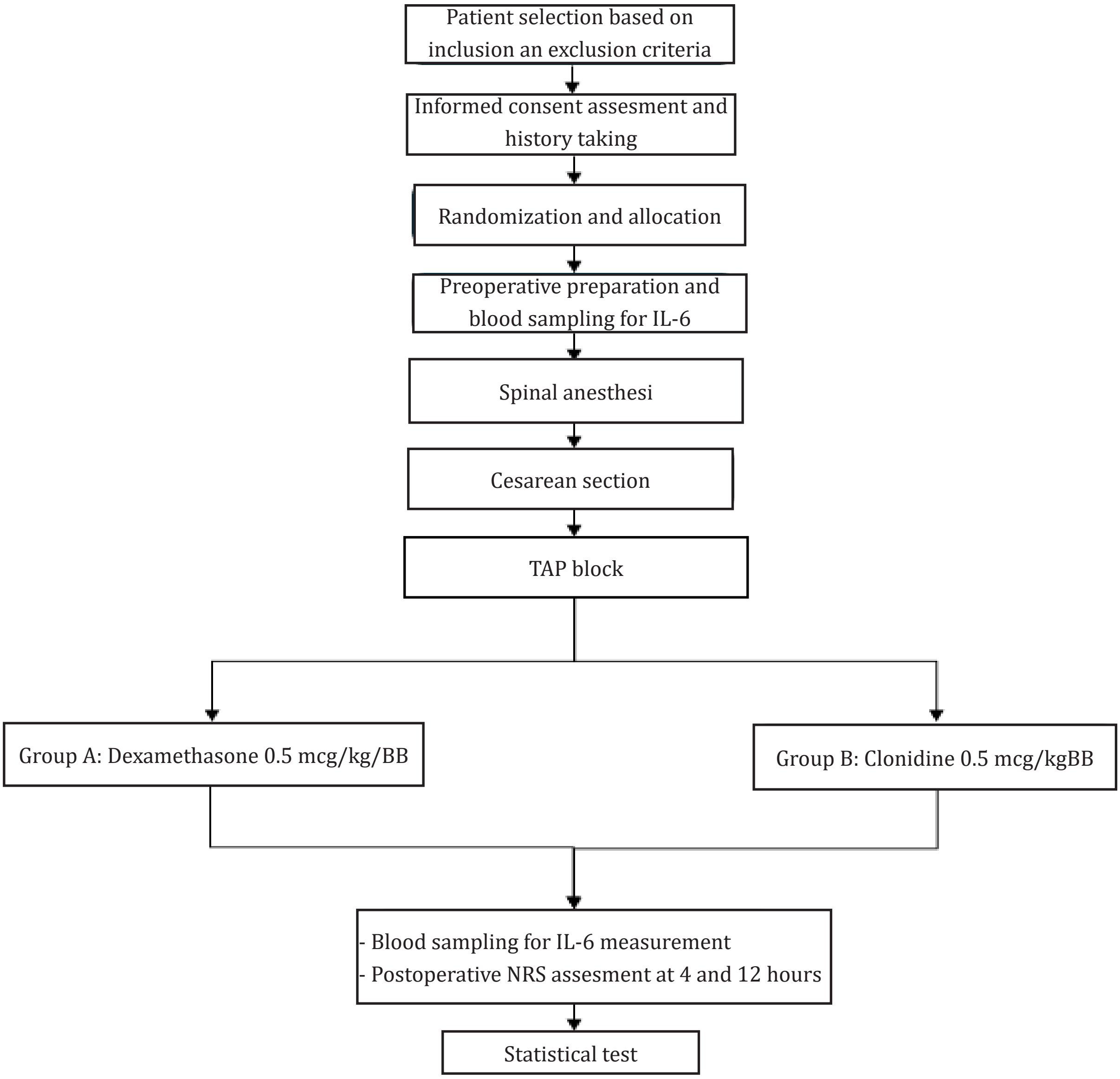

Figure 1 Research Flow Chart

Group A (Dexmedetomidine) showed mean NRS at 4 and 12 hours of 1.93±0.80 and 4.47±0.99, respectively. The mean change in NRS was 2.53±1.19. Group B (Clonidine) showed mean NRS at 4 and 12 hours of 2.07±0.80 and 6.67±0.82, respectively. The mean change in NRS was 4.60±0.99.

Paired difference test showed a significant increase in NRS in both groups, with Group A experiencing a smaller increase compared to Group B. Independent test results showed a significant difference in NRS change between the two groups ($p<0.001$), indicating that dexmedetomidine was more effective at preventing an increase in NRS.

Baseline and 12-hour postoperative serum IL-6 levels were compared between the two groups. In Group A (Dexmedetomidine), the mean preoperative IL-6 level was 15.10±5.90 pg/mL, and the mean IL-6 level at 12 hours postoperatively was 6.04±2.29 pg/mL, with a mean change of –9.06±6.23 pg/mL. In Group

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Table 1 Demographic Characteristics of the Study

Baseline Characteristics	Total (n=30)	Group A (dexmedetomidine) (n=15)	Group B (clonidine) (n=15)	p-value
Age (mean±SD)	31.57±4.11	32.00±4.69	31.13±3.54	0.573[a]
BMI (mean±SD)	28.43±2.86	28.07±1.98	28.80±3.75	0.850[b]

Note: Numerical data observation results are described as mean±SD; [a]difference test for unpaired groups with normally distributed numerical data (independent t-test);[b]difference test for unpaired groups with non-normally distributed numerical data (Mann-Whitney)

B (Clonidine), the mean preoperative IL-6 level was 14.52±6.23 pg/mL, and the mean IL-6 level at 12 hours postoperatively was 10.17±3.68 pg/mL, with a mean change of -4.35±5.86 pg/mL. Paired difference test showed a significant decrease in IL-6 in both groups, with Group A showing a greater decrease than Group B. Independent test results showed a significant difference in IL-6 change between the two groups (p=0.042), indicating that dexmedetomidine was more effective in reducing IL-6 levels.

Administration of dexmedetomidine 0.5 mcg/kg as an adjuvant to TAP block was more effective in preventing NRS increase and reducing IL-6 levels compared to administration of clonidine 0.5 mcg/kg as an adjuvant to TAP block.

Discussion

Although long-term neuraxial techniques

Table 2 Difference Test of NRS in Both Groups

Group	NRS		p-value	Delta NRS
	4 hours	12 hours		
Group A (dexmedetomidine)	1.93±0.80	4.47±0.99	0.001*[c]	2.53±1.19
Group B (clonidine)	2.07±0.80	6.67±0.82	0.001*[c]	4.60±0.99
p-value	0.643[a]	<0.001*[a]		<0.001*[b]

Note: Observation results are described as mean± SD, [a]difference test for unpaired groups not meeting normality requirements (Mann-Whitney); [b]difference test for unpaired groups meeting normality requirements (independent t-test); [c]difference test for paired groups meeting normality requirements (paired t-test); [d]difference test for paired groups not meeting normality requirements (Wilcoxon rank test). * Declared significant if the test produces p<0.05

Table 3 Difference Test of IL-6 in Both Groups

Group	IL 6		p-value	Delta IL-6
	Pre	12 hours		
Group A (dexmedetomidine)	15.10±5.90	6.04±2.29	<0.001*[b]	-9.06±6.23
Group B (clonidine)	14.52±6.23	10.17±3.68	0.012*[b]	-4.35±5.86
p-value	0.795[a]	0.001*[a]		0.042*[a]

Note: Observation results are described as mean±SD, [a]difference test for unpaired groups meeting normality requirements (independent t-test); [b]difference test for paired groups meeting normality requirements (paired t-test). * Declared significant if the test produces p<0.05

or patient-controlled epidural/intravenous opioids are effective in managing pain, they often cause side effects such as nausea, vomiting, and pruritus, which reduce patient satisfaction.[23] Hydrophilic opioids such as morphine can cause delayed respiratory depression in mothers, and logistical challenges or medical contraindications also limit neuraxial opioid use. Lipophilic opioids such as pethidine excreted in breast milk can cause transient adverse effects on newborns. Given these challenges, regional techniques such as the transversus abdominis plane block (TAP block) have the potential to provide effective and prolonged analgesia after cesarean section.[18]

TAP block is a modern regional anesthesia technique that reduces postoperative pain in the anterolateral abdominal region. The type and concentration of local anesthetic in the TAP block have been modified to prolong postoperative pain relief. Alternative methods involve adding adjuvants to local anesthetic solutions. Several adjuvants, such as α2 agonists, dexamethasone, magnesium, and epinephrine, have been investigated, with dexmedetomidine and clonidine being adjuvants known for their analgesic properties.[24]

This study compared the effectiveness of TAP blocks with adjuvants of dexmedetomidine and clonidine for postoperative pain and inflammation management. Study results showed that both adjuvants significantly reduced postoperative pain intensity. Dexmedetomidine was more effective than clonidine in prolonging analgesia duration and reducing rescue analgesic requirements.[13,25] Meta-analysis studies also show that dexmedetomidine is more effective in reducing postoperative opioid consumption.[17]

Dexmedetomidine has a longer analgesic duration than clonidine, with significant anti-inflammatory effects through modulation of cytokine release and immune cell activity. Increased postoperative stress markers in the control group indicate a higher stress response compared to the dexmedetomidine group.[26,27] Previous study found that when intravenous dexmedetomidine was used concurrently with general anesthesia for elective open gastrectomy, a similar intraoperative stress response inhibition was demonstrated by decreased plasma concentrations of norepinephrine, epinephrine, cortisol, tumor necrosis factor-α (TNF-α), and IL-6 compared with combined general and epidural anesthesia.[28]

In this study, serum IL-6 was measured at 12 hours postoperatively, a time point selected based on the known temporal kinetics of IL-6 following surgical trauma. In cesarean section, IL-6 levels have been reported to peak between 12 and 24 hours, followed by a gradual decline toward baseline by approximately 48 hours postoperatively. Thus, measurement at 12 hours postoperatively captures the inflammatory response at or near its peak, providing a representative snapshot of the magnitude of the acute inflammatory response and the anti-inflammatory effects of the adjuvants studied.[29]

It must be emphasized that in this study, NRS pain scores were measured only at 4 and 12 hours postoperatively, whereas IL-6 levels were measured at a single postoperative time point. This approach, with limited time points, provides meaningful insights into the effectiveness of both adjuvants during the early postoperative recovery phase, but does not capture the complete dynamics of analgesic and inflammatory responses. Serial measurements or long-term monitoring with multiple time points (for example, at 6, 12, 24, 48, and 72 hours postoperatively for NRS, and IL-6 measurements at 6, 12, 24, and 48 hours postoperatively) could provide more comprehensive understanding of the full duration of analgesic effects, the timing of peak and decline of IL-6 levels, and the relationship between inflammatory modulation and clinical pain improvement in the postoperative period.

This study makes meaningful contributions to the literature on TAP block adjuvants by using dual outcomes (subjective and objective). The main strengths include solid methodology, sample homogeneity, and IL-6 measurement as an objective biomarker.

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However, this study has limitations, including variability in surgical procedures, short follow-up duration, and the use of IL-6 as an inflammatory marker that reflects only one aspect of the complex immune cascade. The analgesic protocol was not detailed, so the contribution of TAP block adjuvants to integrated pain management could not be fully evaluated. Therefore, the findings of this study require further validation through multicenter studies with larger sample sizes and longer follow-up periods.

Conclusion

Administration of dexmedetomidine 0.5 mcg/kg as an adjuvant to TAP block was more effective than clonidine 0.5 mcg/kg in reducing IL-6 levels and NRS.

Future research needs to evaluate additional inflammatory markers to clarify the effects of adjuvants in these procedures. Longer patient follow-up is also needed to understand parameter changes over time, supporting a better understanding of postoperative pain management and necessary interventions. Variability in surgical techniques used should be considered to comprehensively understand the distribution of analgesic effects of the TAP block with adjuvants.

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