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Correlation between pain intensity and inflammatory biomarkers IL-6 and IL-2 in cesarean section patients under spinal anesthesia using standard analgesia at prof. Dr. I.G.N.G. Ngoerah general hospital

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Abstract

Background: Postoperative pain remains one of the major challenges in post-cesarean section management. Spinal anesthesia is often chosen as the primary anesthetic technique due to its ability to reduce stress and inflammatory responses following surgery. This study aims to investigate the correlation between pain intensity and the levels of IL-6 and IL-2 in patients undergoing cesarean section with spinal anesthesia and standard analgesia.

Methods: This is an analytical observational study designed to analyze the correlation between pain intensity and IL-6 and IL-2 levels in cesarean section patients receiving spinal anesthesia and standard analgesia. Data were collected by measuring pain scores (NRS) and cytokine levels preoperatively and 24 hours postoperatively. Correlations were analyzed using the Spearman test, and changes in the IL-6/IL-2 ratio were compared between the preoperative and postoperative phases.

Results: The study showed that the majority of patients experienced mild to moderate postoperative pain (mean NRS = 3.76). There was a significant positive correlation between postoperative pain intensity and IL-6 levels ($p = 0.030$), supporting the role of IL-6 as an inflammatory mediator associated with pain. However, no significant correlation was found between pain and IL-2 levels ($p > 0.05$). The IL-6/IL-2 ratio between the preoperative and postoperative phases showed no significant difference ($p = 0.339$).

Conclusion: There is a correlation between pain intensity (NRS) and IL-6, but no significant correlation between NRS and IL-2. The changes in the IL-6/IL-2 ratio before and after surgery also showed no significant difference.

Keywords: Postoperative Pain; Cesarean Section; Inflammatory Biomarkers; Spinal Anesthesia; Multimodal Analgesia; Pain-Inflammation Correlation.

1. Introduction

Pain following cesarean section triggers an inflammatory response that increases pro-inflammatory cytokines. IL-6 and IL-2 are known to play roles in immune response, wound healing, and pain. IL-6 is a pro-inflammatory cytokine expected to decrease postoperatively, in contrast to IL-2, an anti-inflammatory cytokine involved in immunity and healing. The IL-6/IL-2 ratio reflects immune response balance and helps assess postoperative healing.

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Tissue damage from cesarean surgery causes the release of inflammatory cytokines such as IL-6 and IL-2. IL-6 recruits immune cells and contributes to postoperative hyperalgesia. IL-2, on the other hand, is involved in tissue remodeling, wound healing, and reducing inflammatory pain. Understanding the dynamics of these cytokines provides insight into postoperative pain and the efficacy of spinal anesthesia combined with standard analgesia.

Effective postoperative pain management improves mobility, shortens hospital stays, and increases patient satisfaction. Multimodal analgesia—using drugs with different mechanisms—offers advantages such as reducing opioid needs, improving pain control, and minimizing side effects like gastrointestinal or CNS disturbances.

2. Methods

This was an analytical observational cross-sectional study aimed at assessing pre- and postoperative levels of IL-6 and IL-2, measuring postoperative pain intensity using the NRS, and analyzing correlations between pain and inflammatory biomarkers in cesarean section patients receiving spinal anesthesia and standard analgesia.

Inclusion criteria: Female patients aged 18–45 years undergoing cesarean section with spinal anesthesia, classified as ASA physical status I–III. Exclusion criteria: Patients with allergies or contraindications to anesthesia or analgesics, autoimmune/systemic diseases affecting inflammation (e.g., HIV, SLE, hypertension, diabetes, asthma), or those unwilling to participate. Dropout criteria: Failed spinal block requiring alternative anesthesia, ICU admission with ventilator post-op, or patients experiencing side effects or death during the study.

2.1. Statistical analysis

Descriptive statistics summarized subject characteristics and variables. Numerical variables were presented as mean ± SD (if normally distributed) or median and IQR (if not). Categorical variables were reported as relative frequencies.

Normality was tested using Kolmogorov-Smirnov. Data were considered normally distributed if $p > 0.05$. Pearson correlation was used for normally distributed variables, otherwise Spearman's correlation was applied. Correlation results included scatter plots and correlation coefficients. Data analysis was performed using SPSS version 26.0.

3. Results

A total of 21 samples were analyzed.

Tabel 1 Characteristics of research samples

Charateristic of Samples (N=21)	**n (%)**
Age (*Mean ± SD*)	29.38 ± 7.11 tahun
ASA	
ASA II	16 (76.19%)
ASA III (Preeclampsia)	5 (23.8%)
Spinal Anesthesia	
Bupivacaine 12.5 mg	21 (100%)
Post-op Analgesia	
Fentanyl	8 (38.1%)
Morfin	13 (61.9%)

*univariate test

Pain was assessed 24 hours postoperatively. The median NRS at rest was 1.00 (IQR: 1.0–3.0) and during movement was 3.00 (IQR: 3.0–5.0), indicating mild to moderate pain.

Tabel 2 Pain intensity before and after cesarean section

Pain intensity	Median (min-max)
NRS Post operative (moving)	3.00 (3.0 – 5.0)
NRS post-operative (resting)	1.00 (1.0 – 3.0)

*univariate test

- Blood samples were collected pre-op and 24 hours post-op to measure IL-6 and IL-2. Neither biomarker was normally distributed ($p < 0.05$).
- IL-6 significantly decreased post-op: from 55.61 (41.95–201.39) pg/mL to 52.87 (27.77–81.04) pg/mL ($p = 0.040$).
- IL-2 also significantly decreased: from 236.32 (143.02–379.40) to 213.68 (141.77–389.47) pg/mL ($p = 0.012$).
- The IL-6/IL-2 ratio changed from 0.24 (0.15–0.75) to 0.23 (0.17–0.35), but this change was not significant ($p = 0.339$).

Tabel 3 Inflammatory cytokine levels and IL-6/IL-2 ratio before and after cesarean section

Inflammation Biomarker	Median (min-max) (pg/mL)	*p-value*
IL-6 level		
Pre-operative	55.61 (41.95 – 201.39)	0.040
Post-operative	52.87 (27.77 – 81.04)	
IL-2 level		
Pre-operative	236.32 (143.02 – 379.40)	0.012
Post-operative	213.68 (141.77 – 389.47)	
IL-6/ IL-2 ratio		
Pre-operative	0.24 (0.15 – 0.75)	0.339
Post-operative	0.23 (0.17 – 0.35)	

* wilcoxon test

There was a significant correlation between NRS and IL-6 levels post-op ($p = 0.030$, $r = 0.475$), indicating a moderate correlation—higher pain was associated with higher IL-6. Delta IL-6 also correlated significantly with NRS ($p = 0.004$, $r = -0.596$), suggesting that greater reductions in IL-6 were associated with lower pain scores.

Tabel 4 Correlation of pain intensity with IL-6 levels

Variables	Median (min-max)	Corelation coefficient	*P value*
IL-6 Post operative	52.87 (27.77 – 81.04)		
		0.475	0.030
NRS Post operative			
	3.00 (3.0 – 5.0)		
Delta IL-6	4.49 (-23.80 – 133.10)		
NRS Post operative	3.00 (3.0 – 5.0)	-0.596	0.004

*Spearman correlation test

No significant correlation was found between NRS and IL-2 post-op ($p = 0.406$) or delta IL-2 ($p = 0.297$).

Tabel 5 Correlation of pain intensity to IL-2 levels

Variables	Median	Variables	Median
IL-2 Post operative	213.68 (141.77 – 389.47)	0.068	0.406
NRS Post operative	3.00 (3.0 – 5.0)		
Delta IL-2	9.90 (-15.57 – 86.32)		
		-0.239	0.297
NRS Post operative	3.00 (3.0 – 5.0)		

*Spearman correlation test

4. Discussion

This study aimed to examine the correlation between pain intensity and the inflammatory biomarkers IL-6 and IL-2 in cesarean section patients who received spinal anesthesia and standard analgesia at Prof. Dr. I.G.N.G. Ngoerah General Hospital. It explored and analyzed the relationship between postoperative pain intensity and the levels of inflammatory cytokines IL-6 and IL-2 in patients undergoing cesarean section using spinal anesthesia and standard analgesia protocols.

From the demographic data collected, the majority of the study samples were young adults, with a mean age of 29.38 years. Most patients were classified as ASA II, indicating relatively stable medical conditions prior to surgery. This distribution is consistent with literature findings that show ASA II patients typically have a lower risk of postoperative complications.[3]

Postoperative pain intensity, as measured by the movement NRS score, had a median of 3.00 (3.0–5.0). More than half of the patients reported pain levels in the range of 3 to 5 on the NRS, which indicates mild to moderate pain. This aligns with existing literature suggesting that postoperative pain is among the most frequently reported symptoms, with peak intensity often occurring within the first 24 hours after surgery.[7] Most patients experienced moderate pain (NRS 3–4) on the first day after cesarean section, which generally decreases over time as the healing process progresses. Resting pain is often associated with surgical injury, while movement-related pain tends to be more intense due to physical activity involving the affected area.[8,9]

The IL-6 levels decreased from 62.58 pg/mL preoperatively to 51.21 pg/mL postoperatively, indicating an inflammatory process occurring during and after the surgical procedure. IL-6 plays a key role in the acute inflammatory response, and elevated IL-6 levels are often associated with postoperative pain. IL-6 levels typically peak within the first few hours following surgery as part of the body's response to surgical trauma. However, within 24 hours, although IL-6 remains elevated, healing and regulatory mechanisms begin to take place, causing a gradual decrease.

This reduction in IL-6 may be due to negative feedback regulation via anti-inflammatory cytokines such as IL-2 and TGF-β, which inhibit pro-inflammatory pathways, including IL-6 production. Additionally, enhanced immune system regulation and tissue regeneration also help reduce IL-6 levels as inflammation and tissue damage subside. This process is part of the inflammatory resolution required for recovery after surgical trauma.[10,11]

Moreover, the reduction in IL-6 may also be influenced by the use of opioids, NSAIDs, and paracetamol postoperatively. NSAIDs inhibit COX enzymes, directly reducing prostaglandin and IL-6 production, and lowering systemic inflammation. Opioids, while effective in reducing pain, may suppress IL-6 production through opioid receptors on immune cells—though this effect can vary depending on the type and dosage of opioid used (Sutariya et al., 2023). Paracetamol, with milder analgesic effects, may indirectly reduce IL-6 by alleviating pain and physiological stress, though its anti-inflammatory effect is weaker than NSAIDs.[5,6]

Postoperatively, IL-2 levels showed a non-significant decrease, from 237.05 pg/mL to 218.81 pg/mL. This reduction does not necessarily reflect a weakened immune function but rather a modulation of the immune system after surgery. IL-2 plays a key role in T-cell proliferation and differentiation, which are essential for adaptive immune responses. Its

concentration is typically influenced by the body's need to regulate long-term immune reactions after trauma or surgery. In the early postoperative phase, the acute inflammatory response, dominated by pro-inflammatory cytokines like IL-6, takes precedence, whereas IL-2 is more involved in targeted immune regulation. The non-significant decline in IL-2 suggests that despite acute inflammation, the immune system continues to maintain a balance between activation and suppression to prevent excessive tissue damage.[1,6]

Correlation analysis revealed a significant relationship between postoperative NRS pain scores and IL-6 levels at 24 hours post-op ($p = 0.030$). This supports IL-6's role as a key mediator in the inflammatory process associated with pain. IL-6 is instrumental in pain sensitization, especially following injury or surgery. It interacts with central and peripheral nervous system receptors, enhancing neuronal sensitivity to pain stimuli. Elevated IL-6 can also stimulate the release of other inflammatory mediators such as prostaglandins, which amplify inflammation and pain. Furthermore, IL-6 contributes to immune cell infiltration (e.g., macrophages) at the injury site, exacerbating local inflammation and increasing peripheral pain sensitivity. IL-6 also affects the spinal cord—the central pain processing hub—by increasing pain signal transmission to the brain. Recent studies suggest that IL-6 inhibition may reduce postoperative pain sensitization, presenting a potential therapeutic target.[8,9] This significant correlation indicates that postoperative inflammation may directly contribute to higher pain levels experienced by patients.

From the IL-6/IL-2 ratio perspective, the study compared pre- and postoperative levels of IL-6 and IL-2 to assess the interplay between these cytokines during healing. The data showed a decrease in the IL-6/IL-2 ratio postoperatively, but this change was not statistically significant ($p = 0.339$). The IL-6/IL-2 ratio reflects the balance between acute inflammatory response (IL-6) and adaptive immune regulation (IL-2). A high IL-6/IL-2 ratio post-op indicates dominant acute inflammation, which may delay healing and increase the risk of complications like infection and persistent pain. Conversely, a lower ratio suggests a shift toward recovery, with more balanced immune regulation. Recent research indicates that a high IL-6/IL-2 ratio is associated with worse postoperative outcomes, whereas a lower ratio is linked to faster recovery and more efficient immune responses.[10]

5. Conclusion

This study found a correlation between pain intensity (NRS) and IL-6 levels but no significant correlation between NRS and IL-2. Additionally, there was no significant change in the IL-6/IL-2 ratio between the preoperative and postoperative phases.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclsoed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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