JUSINDO, Vol. 8 No. 1, June 2026
p-ISSN: 2303-288X, e-ISSN: 2541-7207

Comparison of Continuous Fentanyl and Levobupivacaine Epidural Anesthesia for Perioperative Pain Following Laparotomy in Children Aged 6– 12 Years

Bahtiar Ahmad*, Kohar Hari Santosa, Arie Utariani, Lucky Andriyanto
Universitas Airlangga, Indonesia
Email: bahhyamor@gmail.com*, arieutariani1955@gmail.com, lky.anest@gmail.com, koharhs@yahoo.com

Keywords:
pediatric anesthesia; postoperative pain; epidural analgesia; fentanyl; levobupivakain

Abstract

Postoperative pain management in pediatric patients is a clinical challenge because uncontrolled pain can trigger systemic inflammatory responses, slow recovery, and increase the risk of postoperative morbidity. Surgical trauma stimulates the release of proinflammatory cytokines such as interleukin-6 (IL-6) and affects hematologic inflammatory parameters, including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). This study aimed to assess differences in the effectiveness of continuous fentanyl administration and epidural levobupivacaine on inflammatory responses and postoperative pain intensity in pediatric patients undergoing laparotomy. This comparative analytical study involved 30 pediatric patients aged 6–12 years who underwent elective laparotomy and were divided into two groups, namely continuous fentanyl (n=15) and epidural levobupivacaine (n=15). The parameters assessed included IL-6, NLR, and PLR levels, as well as pain intensity using the Numerical Rating Scale (NRS), which was measured in the preoperative and postoperative periods. Statistical analysis was conducted to assess differences within and between groups. The baseline characteristics of the subjects were homogeneous (all $p>0.05$). The median PLR increased from 136.2 (79.5–411.4) to 161.3 (90.6–616.2) ($p=0.106$), and the median NLR increased from 1.98 (0.98–19.94) to 2.11 (0.80–28.91) ($p=0.643$), with no significant differences between groups. IL-6 levels increased significantly overall ($p=0.018$), significantly in the fentanyl group ($p=0.028$) but not in the levobupivacaine group ($p=0.225$). NRS scores decreased significantly in both groups ($p<0.001$), with a greater reduction in the epidural levobupivacaine group in the early postoperative period (ΔNRS −4 vs −3.07±1.10; $p=0.030$). Both analgesic modalities were effective in reducing postoperative pain. Epidural levobupivacaine provided better early postoperative pain control and showed a more stable inflammatory response profile compared with continuous fentanyl..

INTRODUCTION

Postoperative pain management in pediatric patients is a complex challenge, as inadequate care can have both physiological and psychological impacts. A study in Ethiopia involving 154 pediatric patients reported that the prevalence of overall postoperative pain reached 83.7% at 6 hours after surgery, with moderate-to-severe pain at 38.9%. In a systematic review, the prevalence of chronic postoperative pain ranged from 20% to 30%. Surgical tissue injury triggers an inflammatory response characterized by increased proinflammatory cytokines, including interleukin-6 (IL-6) (Mankelkilot & Berhane, 2025; Sim et al., 2024), tumor necrosis factor-alpha (TNF-α), and interleukin-1β. This cytokine elevation increases nociceptive sensitivity and contributes to both acute and chronic postoperative pain (Gómez-Ríos et al., 2022). Inflammatory biomarkers such as the neutrophil-to-lymphocyte ratio (NLR)

and platelet-to-lymphocyte ratio (PLR) function as indicators of systemic inflammation, providing an overview of postoperative inflammatory status. The inflammatory response also activates the sympathetic nervous system and influences recovery outcomes (Gómez-Ríos et al., 2022).

Due to the limited ability of children to express pain verbally, objective assessment instruments are essential. The Numerical Rating Scale (NRS) is a valid and reliable tool for assessing acute pain in pediatric perioperative settings (Hassan et al., 2021). The advantage of the NRS lies in its simplicity and sensitivity in detecting changes in pain intensity, making it more practical than many observational methods. Not only does this scale facilitate measurable assessment of pain, but when combined with inflammatory biomarkers such as IL-6, NLR, and PLR, it also provides a more comprehensive understanding of postoperative status and the effectiveness of analgesic strategies.

The importance of opioid-free anesthesia strategies in pediatric elective surgery is increasingly emphasized because the systemic side effects of opioids can affect a child's recovery and quality of life. Regional analgesia can be an effective alternative to minimize systemic opioid use by providing localized pain control, thereby reducing opioid-related adverse effects. However, epidural anesthesia techniques require specialized expertise and are contraindicated in conditions such as coagulopathy and local infections, which can limit their application (Erten, 2024; Boretsky, 2019). The pharmacological mechanisms of levobupivacaine and fentanyl differ: levobupivacaine blocks sodium channels, thereby interrupting pain transmission and potentially modulating inflammatory responses, which may support recovery without the systemic side effects typical of opioids (de Boer et al., 2019). In contrast, fentanyl acts centrally via μ-opioid receptor agonism to provide significant analgesia; however, potential immunosuppressive effects at high doses remain a concern. To date, there have been no studies comparing continuous fentanyl administration with epidural analgesia in pediatric surgical patients, particularly in relation to inflammatory biomarkers such as IL-6, NLR, and PLR (Erten, 2024; Ghobrial & Shaker, 2019).

There have been no studies specifically comparing continuous fentanyl and epidural levobupivacaine in pediatric patients in relation to IL-6, NLR, PLR, and NRS scores. This study aims to assess the effectiveness of both modalities in controlling pain and reducing postoperative inflammatory responses in children undergoing elective surgery.

METHOD

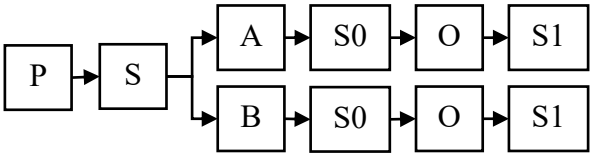
Types and Research Designs

Types of research

This study was a quantitative research with a quasi-experimental design. It aimed to compare continuous fentanyl administration and epidural levobupivacaine analgesia in relation to postoperative interleukin-6 (IL-6) levels, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and numerical rating scale (NRS) scores in pediatric patients undergoing laparotomy.

The study subjects were divided into two groups: a continuous fentanyl group and an epidural levobupivacaine group. IL-6, NLR, PLR, and NRS were measured preoperatively and postoperatively.

Research design



Picture 0.1 Research design

Description:

P : Population

S : Sample

A : Group A, receive *fentanyl* continuous

B : Group B, receive Epidural analgesia *levobupivacaine*

S0 : Blood sampling before surgery

O : Operation laparatomi

S1 : Blood sampling after Operation

Place and Time of Research

This research was conducted in the Surgery Room and Postoperative Care Room at the Hj. Anna Lasmanah Regional General Hospital (RSUD), Banjarnegara Regency, Central Java. The research was conducted in the period between July-August 2025.

Population and Research Sample

Research population

The population of this study was pediatric patients undergoing elective surgery. The patients who became the population were patients who were in the Hj. Anna Lasmanah Hospital, Banjarnegara Regency, Central Java during the research period.

Research sample

The research sample was selected based on predetermined inclusion and exclusion criteria to ensure the validity and reliability of the research results.

Inclusion criteria

1. Pediatric patients aged 6 to 12 years who are scheduled to undergo a lower abdominal laparotomy procedure.
2. Patients with ASA (*American Society of Anesthesiologists*) I–II physical status.
3. Patients with adequate nutritional status.
4. Patients with surgery duration of about two hours

Exclusion criteria

1. Patients with a history of allergy to *fentanyl* or the epidural anesthetic drug *levobupivacaine*.
2. Patients with coagulation disorders, local/spinal infections, or neurological disorders that are contraindicated for epidural procedure.
3. Patients with a history of complex congenital heart disease, autoimmune disease, or active systemic infections.

Drop-out *criteria*

1. Patients who experience during the procedure:

a. Failure of a block or an elongated operation (resulting in a change in anesthesia technique)

b. *High* or *Total Spinal Block*

c. Bleeding of more than 20% EBV
2. Incomplete research data

Sampling

Sampling techniques

The sampling technique was carried out by *the consecutive sampling* method. *Consecutive sampling* is that all patients who meet the inclusion criteria and are not included in the exclusion criteria will be included in the study until the sample number is met.

Sample size

With the experimental research *design pre-post test control group design*, the minimum sample size is calculated with the following formula: (Walters et al., 2019)

$$n = \frac{2\sigma^2(Z_{1-\alpha/2} + Z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$$

n : the minimum number of samples required in each group.

$Z_{1-\alpha/2}$: The value of the standard normal distribution (table Z) at a given alpha (0.05 = 1.96)

$Z_{1-\beta}$: The value of the standard normal distribution (table Z) at a given beta (80% = 0.84)

σ^2 : The IL-6 variance price in the population in the previous study was 40 pg/mL (Lin et al., 2025)

$\mu_1 - \mu_2$: Difference *red* The IL-6 in population 1 and population 2 in the previous study was 47 pg/mL (Lin et al., 2025) .

$$n = \frac{2(40^2)(1.96 + 0.84)^2}{(47)^2}$$

$$n = \frac{3200 \times (2.8)^2}{2209}$$

$$n = \frac{25088}{2209}$$

$$n = 11{,}357$$

To anticipate the sample that *dropped out*, a correction factor of 30% was used, so that the number of samples in each group was 14.76 with rounding up to 15 research subjects.

Research Variables

Bound variables

The bound variables in this study were IL-6, NLR, PLR, and NRS levels measured before and after surgery.

Independent variables

The independent variable in this study was continuous *fentanyl* administration or epidural analgesia *levobupivacaine*. Group A will receive continuous *fentanyl, while group B will receive* levobupivacaine *epidural analgesia*.

Confusing variables

This study can have confounding variables starting from age, nutritional status, duration of surgery, type of surgery, history of comorbidities, and patient status during surgery (blood pressure, average MAP, $EtCO_2$).

Variable operational definition

Table 0.1 Variable operational definition

Yes	Variable	Operational Definition	Measuring Instruments	How to Measure	Measurement Results	Scale
1	IL-6 Levels	Concentration of IL-6 in the blood as an indicator of postoperative inflammation	ELISA	Blood sampling before surgery and shortly after surgery before extubation	pg/mL	Ratio
2	NLR	Ratio of neutrophils to lymphocytes as an indicator of inflammatory response	Complete blood count	Blood sampling before surgery and shortly after surgery before extubation	Ratio	Ratio
3	PLR	Ratio of platelets to lymphocytes as an indicator of inflammation	Complete blood count	Blood sampling before surgery and shortly after surgery before extubation	Ratio	Ratio
4	Pain level	Patient pain score based on the NRS scale	NRS Scale	Assessment of pain scale from 0 (no pain) to 10 (very severe pain) before surgery, shortly after extubation, and one hour after extubation	0-10	Ratio
5	*Fentanyl* continues	Continuous infusion *of fentanyl* at a dose of 0.5 μg/kg/hour as analgesia during surgery.	*Syringe pump*, dosage record	During the operation	μg/kg/h	Ratio
6	Epidural analgesia	Continuous administration of *levobupivacaine* 0.125% via epidural catheter	*Syringe pump*, dosage record	During the operation	mL/hour	Ratio

Research Procedure

1. Patients who meet the inclusion criteria will be given an explanation of the purpose and procedure of the study, then asked to sign *an informed consent* by a parent/legal guardian.
2. The patient was described about the anesthesia plan of action and the study procedure included continuous *administration of fentanyl* or *epidural levobupivacaine* after anesthesia induction and blood collection at certain times.
3. All patients who met the inclusion criteria would be included in the study. If the patient in the course of his illness during the study has the criteria for expense, the patient will be excluded from this study.
4. Patients were divided into two groups, namely group A (*continuous fentanyl*) or group B (*epidural levobupivacaine*)
5. Before surgery, in the medical room, a re-examination of the patient's identity, diagnosis, *informed consent* anesthesia is carried out.

6. Basic patient data was collected, including demographic characteristics, medical history, and initial laboratory examination of IL-6, NLR, and PLR levels before surgery (preoperative).
7. After the patient enters the operating room, standard monitors including ECG, non-invasive blood pressure, breathing rate, and oxygen saturation are installed. The patient was then administered general anesthesia according to hospital standards, with induction using the sedative agent midazolam, an induction agent with propofol, pre-intubated local analgesics with *lidocaine* spray, and atracurium muscle relaxants, followed by airway installation and mechanical ventilation. Anesthesia maintenance is carried out using inhaled anesthetic gas with *sevoflurane* and analgesics in accordance with the applicable protocol.
8. After induction, *paracetamol* 10mg/kgBB was administered intravenously to all groups of patients.
9. Group A anesthesia patients used continuous *fentanyl* using *a syringe pump* with a dose of 1 mcg/kgBB/hour. Group B anesthesia patients used *0.125% epidural* levobupivacaine, epidural *puncture* was at Th-12 with a target height as high as Th-6.
10. *Rescue analgetics* are in the form of intravenous *bolus fentanyl* 1 mcg/kgBB fast-onset opioid in group A or 0.125% epidural *levobupivacaine* bolus in group B, and the dose is increased by 25% if there is a suspicion of intra and postoperative acute pain conditions characterized by an increase in pulse > 20 points and/or an increase in MAP > 20% from basal without the involvement of other conditions according to clinical considerations anesthesiologist on duty.
11. After the surgery is completed, the patient is monitored in the recovery room/*post anesthetic care unit* (PACU) with strict monitoring of hemodynamics and pain.
12. Postoperative evaluation is performed instantly, one hour, and two hours after extubation with blood collection for measurement of IL-6, NLR, and PLR levels through blood tests.
13. Pain assessment using the NRS scale is performed after the patient is conscious.
14. Data were collected and analyzed to compare the effectiveness of pain control and inflammatory response between the two intervention groups.

Operational Framework

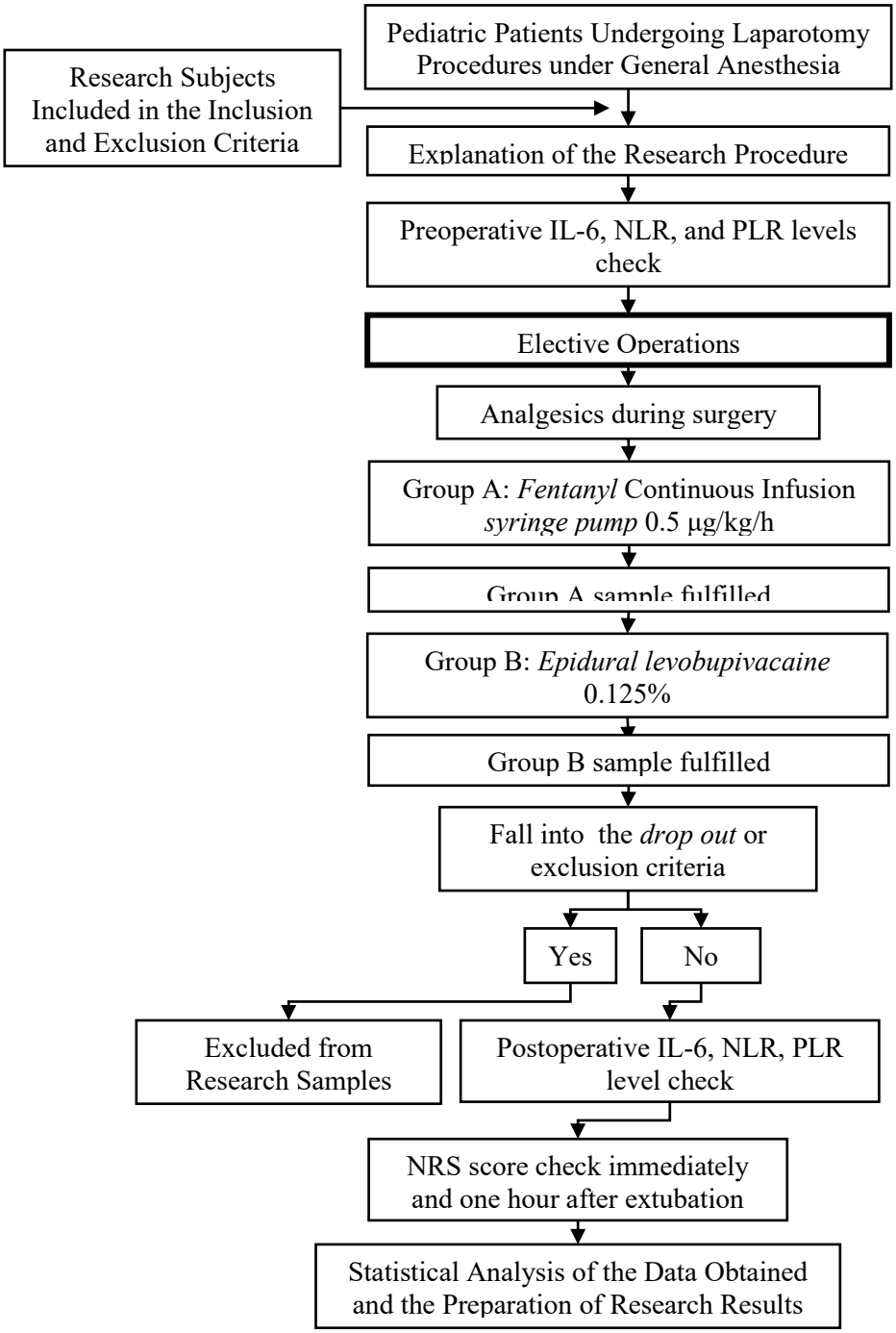


Image 0.2 Operational framework.

Data Processing and Analysis

1. The data collected will be checked for completeness before being analyzed.
2. Demographic data and patient characteristics were tested for data normality using *the Shapiro-Wilk test.*
3. The data is displayed frequency and average as well as standard deviation (normal distributed data) or median and *range* (abnormal distributed data)
4. Changes in IL-6, NLR, and PLR levels before and after the intervention were analyzed using paired t-assays or *Wilcoxon assays*.

5. The comparison of NRS values between treatment groups was analyzed using *the chi-square* test.
6. Statistical significance is determined by *a p-value* < 0.05.
7. All analyses were performed using SPSS statistical software.

Research Ethics

Hj. Anna Lasmanah Hospital, Banjarnegara Regency, Central Java is under the auspices of Gajah Mada University (UGM). This research has been approved by the ethics committee published by UGM.

RESULTS AND DISCUSSION

Characteristics of Research Subjects

Table 0.1 Characteristics of the research subject.

Variable	All Research Subjects (n=30)	Fentanyl (n=15)	Levobupivakain (n=15)	*p-value*
Age (years)	10 (5-12)	8 (5-12)	10 (6-12)	0.850A
Weight (kg)	25,5 (13-56)	20 (13-56)	27 (17-56)	0.429a
Height (cm)	147.37 ± 6,578	147.33 ± 7.697	147.4 ± 5,514	0.978b
Duration of operation (minutes)	89 ± 21,066	89.33 ± 22,824	88.67 ± 19.952	0.933b
NRS Preoperative	6 (4-7)	6 (4-7)	5.53 ± 0.915	0.326a
Type of operation				1,000c
Appendicitis	25 (83,3%)	13 (86,7%)	12 (80%)	
Non-appendicitis	5 (16,7%)	2 (13,3%)	3 (20%)	
Rescue Analgesia				1,000c
Yes	3 (10%)	1 (6,7%)	2 (13,3%)	
No	27 (90%)	14 (93,3%)	13 (86,7%)	

[a] Mann-Whitney test; [b] independent t-test; [C] Chi-Square *Test*

The characteristics of the study subjects showed that the two groups had relatively comparable distributions. The median age in all subjects was 10 years (range 5–12 years), with *the fentanyl* group being slightly younger than *the levobupivacaine* group, but this difference was not statistically significant (p=0.850). Anthropometric parameters were also similar, with a median body weight of 25.5 kg in all subjects and no significant differences between groups (p=0.429). The average height ranged from 147 cm in both groups, with comparable variation (p=0.978).

The duration of the operation showed an average of about 89 minutes across subjects, with an almost identical distribution between *the fentanyl* and *levobupivacaine groups* (p=0.933). The preoperative pain score (NRS) was also not significantly different, with a median of 6 in the fentanyl group and an average of 5.53 in the levobupivacaine group (p=0.326).

Based on the type of surgery, the majority of patients underwent appendicitis in both groups (83.3% overall), with a balanced proportion and no significant differences (p=1,000). Similarly, the use of rescue analgesia showed no significant difference between the two groups, with the vast majority of patients requiring no additional analgesia (90% in all subjects; p=1,000).

Inflammatory Response

Table 0.2 Preoperative IL-6, NLR, and PLR inflammatory response results.

Inflammatory Response	Measurement Values [median (*range*)]	*p-value*[a]
IL-6 (pg/mL)	3,5 (1,76-69,9)	0,761
Fentanyl	3,5 (1,76-67,2)	
Levobupivakain	3,5 (1,76-69,9)	
NLR	1,98 (0,98-19,94)	0,967
Fentanyl	1,91 (0,98-19,94)	
Levobupivakain	2,05 (0,98-19,94)	
PLR	136,2 (79,5-411,4)	0,934
Fentanyl	136,2 (87,7-411,4)	
Levobupivakain	136,2 (79,5-411,4)	

[a] difference test between groups using the Mann-Whitney test

Table 0.3 Postoperative results of IL-6, NLR, and PLR inflammatory responses.

Inflammatory Response	Measurement Values [median (*range*)]	*p-value*[a]
IL-6 (pg/mL)	3,5 (1,69-134)	0,639
Fentanyl	3,5 (1,96-134)	
Levobupivakain	3,5 (1,69-134)	
NLR	2,11 (0,80-28,91)	0,819
Fentanyl	2,64 (0,80-28,91)	
Levobupivakain	2,05 (0,98-19,94)	
PLR	161,3 (90,6 - 616,2)	0,299
Fentanyl	167,7 (102,5-616,2)	
Levobupivakain	146,47 (90,6-458,3)	

[a] difference test between groups using the Mann-Whitney test

Table 0.4 The results of changes in the inflammatory response of IL-6, PLR, and NLR between preoperative and postoperative responses.

Inflammatory Response	Measurement Values [median (*range*)]	*p-value*[a]
IL-6 (pg/mL)	0 ((-12,2)-71,2)	0,018
Fentanyl	0 ((-0,19)-71,2)	0,028
Levobupivakain	0 ((-12,2)-71,2)	0,225
p-value[b]	0,325	
NLR	0,32 ((-18,9)-27)	0,643
Fentanyl	0,36 ((-18,28)-27)	0,650
Levobupivakain	0,28 ((-18,28)-7,43)	0,865
p-value[b]	0,787	
PLR	13,8 ((-231,3)-528,5)	0,106
Fentanyl	16,4 ((-231,3)-528,5)	0,156
Levobupivakain	11,1 ((-231,3)-285,4)	0,394
p-value[b]	0,547	

[a] *p-value* change in the group using the Wilcoxon *signed-rank test*; [b] *p-value* differences between groups using the Mann-Whitney test

Interleukin-6 (IL-6) levels experienced a statistically significant increase after surgery in all subjects (p = 0.018), particularly in the intravenous fentanyl group (p = 0.028), while in the epidural levobupivakain group the increase was not significant (p = 0.225). These findings suggest that surgical action triggers an acute inflammatory response that is reflected through an

increase in the proinflammatory cytokine IL-6, although such responses are not always followed by meaningful changes in cellular ratio-based inflammatory markers.

In the hematology-based inflammatory parameters, namely *platelet-to-lymphocyte ratio* (PLR) and *neutrophil-to-lymphocyte ratio* (NLR), no significant changes were found between the preoperative and postoperative periods, either in the whole subject or after separate analysis by treatment group. The median values of PLR and NLR showed a tendency for postoperative changes, but these changes did not reach statistical significance based on the Wilcoxon *signed-rank test* (overall $p > 0.05$). This indicates that the systemic inflammatory response represented by the peripheral blood cell ratio is relatively stable in the initial postoperative period.

The results of the comparison analysis between groups using the Mann–Whitney test showed that there was no significant difference in preoperative, postoperative, or change (Δ) PLR, NLR, and IL-6 values between the intravenous fentanyl group and the levobupivakain group (overall $p > 0.05$). Thus, although there was an increase in postoperative IL-6 levels in response to physiological inflammation to surgery, the magnitude of the change did not differ significantly between the two groups. This suggests that treatment in both groups did not provide a difference in the modulation of systemic inflammatory markers in the initial postoperative period.

Numerical Rating Scale

Table 0.5 NRS pain scales preoperatively, postoperatively, and one hour postoperatively

Groups	NRS Preoperative	Postoperative NRS	NRS one hour Postoperative	*p-value*
All Research Subjects	6 (4-7)	2 (0-3)	2 (0-3)	<0.001
Fentanyl (n=15)	6 (4-7)	3 (2-4)	2 (1-3)	<0.001
Levobupivakain (n=15)	6 (4-7)	2 (0-3)	1 (0-2)	<0.001

[a] Friedman test

Analysis of changes in *Numeric Rating Scale* (NRS) scores showed a statistically significant decrease in pain intensity from the preoperative to postoperative period and one hour postoperatively, both in all subjects and after being analyzed separately by treatment group. In all study subjects, the median NRS score decreased from 6 (range 4–7) at preoperative to 2 (range 0–3) at postoperative and remained at 2 (range 0–3) at one hour postoperatively, with the results of the Friedman test showing a significant difference ($p < 0.001$).

A similar pattern of decline was also seen in the intravenous fentanyl group, where the median NRS score decreased from 6 (range 4–7) at preoperative to 3 (range 2–4) at postoperative and further decreased to 2 (range 1–3) at one hour postoperative ($p < 0.001$). In the levobupivakain group, the decrease in pain appeared to be more consistent, with the median NRS score reduced from 6 (range 4–7) at preoperative to 2 (range 0–3) at postoperative and subsequently to 1 (range 0–2) at one hour postoperatively ($p < 0.001$). These findings suggest that both intravenous fentanyl and levobupivakain are effective in lowering the intensity of postoperative pain, with a tendency to decrease pain that continues up to one hour postoperatively, especially in the levobupivakain group.

Table 0.6 Changes in NRS pain scale between preoperative, postoperative, and one hour postoperative

Changes in the pain scale	All Research Subjects	Fentanyl (n=15)	Levobupivakain (n=15)	*p-value*[a]
Δ Post-operative	-4 ((-5)-(-1))	-3.07 ± 1.10	-4 ((-5)-(-2))	0,030
Δ one hour postoperative-postoperative	-1 ((-3)-1)	-0.67 ± 1.05	-0.80 ± 1.32	0,780
Δ one hour postoperative-preoperative	-4 ((-6)-(-2))	-3.73 ± 0.88	-5 ((-6)-(-3))	0,380
[a] Mann-Whitney test				

Based on Table 5.6, it can be seen that overall there was a significant decrease in the NRS pain scale after surgery in all study subjects, both in the immediate postoperative period and one hour postoperatively. The decrease in pain from preoperative to postoperative showed a median ΔNRS of −4 in all subjects, indicating a substantial decrease in pain after anesthesia and analgesia interventions. When compared between groups, the epidural levobupivakain group showed a statistically greater reduction in pain than the intravenous fentanyl group in the preoperative to postoperative period, which was indicated by a median ΔNRS −4 (−5 to −2) in the levobupivakain group compared to the average ΔNRS −3.07 ± 1.10 in the fentanyl group, with a statistically significant difference ($p = 0.030$). These findings suggest that epidural levobupivakain is more effective in lowering initial postoperative pain than intravenous fentanyl. However, in the change in pain from postoperative to one hour postoperatively, no significant difference was found between the two groups ($p = 0.780$), indicating that after the initial postoperative phase, the rate of pain reduction was relatively similar between the two interventions. In the analysis of pain changes from preoperative to one hour postoperatively, although the levobupivakain group showed a numerically greater reduction in pain (median −5 compared to −3.73 in the fentanyl group), the difference did not reach statistical significance ($p = 0.380$). Overall, these results corroborate that the main advantage of epidural levobupivakain lies in a greater reduction in initial postoperative pain, whereas in the advanced postoperative phase, the difference in analgesia effectiveness between epidural levobupivakain and intravenous fentanyl becomes less pronounced.

Interleukin-6 Inflammatory Response, Neutrophil-to-lymphocyte ratio, and Platelet-to-lymphocyte ratio

This study showed that laparotomy in pediatric patients aged 6–12 years triggered a systemic inflammatory response detected through changes in IL-6, NLR, and PLR levels in both treatment groups. Surgical tissue trauma is a powerful stimulus for innate immune system activation through the release of *damage-associated molecular patterns* (DAMPs), *toll-like receptor activation*, and NF-κB transcription pathways, all of which lead to increased proinflammatory cytokines, especially IL-6 as the primary postoperative acute phase mediator (Aliyu et al., 2022; Bain et al., 2023).

IL-6 levels experienced a statistically significant postoperative increase in the fentanyl group ($p = 0.028$), while in the epidural levobupivacaine group the change was not significant ($p = 0.225$). IL-6 is a pleiotropic cytokine that increases rapidly within 2–6 hours of tissue injury and is directly correlated with the extent of surgical trauma and the intensity of the neuroendocrine stress response. IL-6 is also known to play a role in the sensitization of peripheral and central nociceptors through activation of the JAK–STAT and MAPK pathways, as well as increased expression of pain receptors such as TRPV1 and NMDA in (Liu et al., 2020) *the dorsal root ganglion* and spinal cord (Kurniyanta et al., 2025).

In the fentanyl group, a still significant postoperative increase in IL-6 reflects the dominance of central modulation through μ-opioid receptor activation. Fentanyl suppresses pain transmission at the spinal and supraspinal levels and reduces sympathetic activation and hypothalamic–pituitary–adrenal (HPA) axis, but does not completely cut off peripheral nociceptive input from the surgical area. As a result, peripheral afferent stimuli can still trigger the release of local and systemic cytokines, including IL-6, even though clinical pain is controlled (Egbuta & Mason, 2021).

In contrast, in the epidural levobupivacaine group, no significant IL-6 changes were found, suggesting that peripheral and spinal nociceptive transmission blockade exerts a protective effect against the amplification of systemic inflammatory responses. Epidural analgesia is able to inhibit the entry of pain impulses into the spinal cord, thereby suppressing the activation of sympathetic reflexes and surgical stress responses more thoroughly than systemic opioids. The sodium channel blockade mechanism by levobupivacaine directly interrupts the transmission of nociceptive signals before reaching the supraspinal integration center, so that the proinflammatory cascade involving IL-6 can be better controlled (Campos-Pérez et al., 2022).

The NLR showed no significant differences between the two groups, either in the preoperative or postoperative phases. The median value of postoperative NLR was in the low–medium range, indicating a relatively controlled systemic inflammatory response. Physiologically, the increase in NLR reflects a combination of neutrophilia due to acute inflammation and relative lymphopenia due to the influence of cortisol as well as post-surgical stress catecholamines. The absence of NLR differences between groups suggests that both analgesia modalities are effective in suppressing systemic stress responses globally. (Gao et al., 2021)

These results are consistent with various pediatric studies that report that significant NLR changes generally occur in surgical procedures with severe inflammation, such as heart surgery with *cardiopulmonary bypass*, whereas in pediatric elective abdominal surgery NLR changes tend to be mild and not always sensitive to differentiating analgesia techniques. Thus, the NLR results in this study reflect more of the characteristics of the surgery and the relatively stable population, rather than the difference in the specific effects of the type of analgesia (Laila et al., 2024; Xu et al., 2019).

Similarly, the PLR also showed no significant differences between the two groups. PLR reflects the interaction between platelets that play a role in inflammation through the release of mediators such as serotonin and growth factors, with lymphocytes as an adaptive immune element. Recent literature states that PLR is more sensitive as a marker of inflammation . Therefore, the relatively stable findings of PLR in this study cannot be interpreted as a parameter failure, but rather reflect the inherent limitations of PLR in detecting differences in mild–moderate acute inflammation in the context of elective pediatric surgery (Zahmatkesh et al., 2023).

Overall, IL-6 has been shown to be a more sensitive biomarker than NLR and PLR in describing the dynamics of postoperative acute inflammatory responses. Although epidural levobupivacaine showed a more stable tendency to control IL-6, the differences between groups did not reach statistical significance. These findings indicate that the main advantage of epidural

levobupivacaine likely lies not in the overall suppression of systemic inflammation, but rather in the clinical output of postoperative pain.

Numerical Pain *Rating Scale*

The results showed a statistically significant decrease in pain intensity in both groups from preoperative to postoperative ($p = 0.001$), with a significantly greater decrease in the epidural levobupivacaine group than continuous fentanyl in the initial postoperative period (median NRS 4→2 vs. mean 3.07±1.10; $p = 0.030$). These findings confirm the clinical advantages of epidural analgesia in the early critical phase after surgery.

Pathophysiologically, the excellence of epidural levobupivacaine can be explained by the sodium canal blockade mechanism that breaks off nociceptive transmission in the A-δ and C fibers before the pain impulse reaches the dorsal corneal spinal cord. This blockade is local and directly prevents central sensitization from the initial perioperative phase, resulting in more comprehensive analgesia in the surgical area. In contrast to levobupivacaine, fentanyl acts predominantly at the supraspinal and spinal levels through μ-opioid receptor agonism, so that although it is effective in suppressing pain perception and emotional responses, peripheral nociceptive afferent inputs can still enter and trigger central sensitization (Egbuta & Mason, 2021; Lavand'homme, 2022) . This explains why the decrease in NRS in the fentanyl group tends to be smaller in the early postoperative phase.

The absence of a significant difference in NRS between the two groups at one hour postoperative ($p = 0.780$) suggests that the analgesia effectiveness of both modalities becomes equivalent over time. Continuous fentanyl is able to provide better analgesic stability in the advanced postoperative phase when the acute pain stimulus begins to decrease and local inflammation enters the initial resolution phase (Franz et al., 2021) . The advantage of epidural levobupivacaine is thus more temporal, that is, it is dominant in the early postoperative phases when peripheral and central sensitization is still very active (Bain et al., 2023).

The use of NRS as a pain assessment instrument in this study can be considered valid, as children aged 6–12 years already have adequate cognitive abilities to understand numerical concepts and report pain intensity consistently. These results are also consistent with various pediatric studies that report that regional anesthesia provides superior pain control over systemic opioids in abdominal surgery, among them Ulrikh et al. (2018) who reported a significant decrease in pain score and the need for additional analgesics with long-term use of local anesthesia, as well as Martínez-López et al. (2022) who showed that epidural analgesia is able to decrease the intensity of early pain and prolong the interval postoperative pain-free. In addition, the tendency for more stable IL-6 control in the epidural levobupivacaine group likely contributed to a faster reduction in pain in the early phases, given that IL-6 plays a role in nociceptor sensitization that aggravates pain perception (Kurniyanta et al., 2025; Tsze et al., 2018)

Overall, these results confirm that epidural levobupivacaine provides a real clinical advantage in lowering the intensity of premature postoperative pain in pediatric patients undergoing laparotomy. Epidural analgesia offers more optimal pain control in the early critical period without having to rely on increasing systemic opioid doses, thus strengthening its position as the primary choice in pediatric postoperative pain management on elective abdominal procedures (Erten, 2024; Lavandhomme, 2022).

Research Implications

The results of this study have important clinical and scientific implications in pediatric postoperative pain management, particularly in school-age patients undergoing laparotomy. The finding that *epidural levobupivacaine* provided a significantly greater reduction in NRS scores in the early postoperative phase, although not accompanied by significant differences in systemic inflammatory biomarkers, confirms that the clinical outcome of pain should be a key parameter in the selection of analgesic techniques in pediatrics. This is in line with the literature that states that successful pain management does not always parallel changes in inflammatory biomarkers, especially in mild–moderate degree acute inflammation (Lavand'homme, 2022) .

Clinically, these results support the use of *epidural levobupivacaine* as an excellent analgesic strategy in pediatric abdominal surgery, especially to optimize preoperative pain control. Better pain control in the early phases is known to lower the risk of central sensitization, accelerate mobilization, and improve pediatric patient comfort and adherence to postoperative care. In addition, reduced dependence on systemic opioids has the potential to lower the risk of opioid side effects such as respiratory depression, oversedation, and ileus, which are major concerns in pediatric anesthesia practice (Bain et al., 2023; Egbuta & Mason, 2021) .

From a scientific point of view, this study highlights the limitations of hematological inflammatory biomarkers such as NLR and PLR in differentiating the effectiveness of analgesation techniques in the context of elective pediatric surgery. These findings encourage a multimodal evaluation approach that integrates subjective clinical parameters, such as NRS, with more specific and sensitive inflammatory biomarkers, such as IL-6. Thus, this study provides the basis for the development of pediatric pain management protocols that are more oriented towards meaningful clinical outcomes and individualization of therapy (Aliyu et al., 2022) .

Research Limitations

This study has several limitations that need to be considered in interpreting the results. First, relatively limited sample sizes and coming from a single healthcare center may limit the generalization of findings to a broader pediatric population with different clinical and demographic characteristics. The variability of inflammatory responses and pain perception in children is strongly influenced by age, nutritional status, psychological condition, as well as variations in surgical techniques, which were not entirely controllable in this study (Zieliński et al., 2020).

Second, measurements of inflammatory biomarkers were limited to IL-6, NLR, and PLR over a specific period of time. The postoperative inflammatory response is dynamic, and IL-6 peaks can vary between individuals depending on the duration of surgery and the degree of tissue trauma. Failure to take serial measurements of IL-6 over longer time intervals may lead to a loss of information regarding the temporal pattern of inflammation more completely. In addition, other inflammatory biomarkers such as TNF-α or ultrasensitive CRP were not evaluated, so the interpretation of the systemic inflammatory response is still partial (Liu et al., 2020).

Third, the use of NLR and PLR as indicators of inflammation has limited sensitivity in the context of mild to moderate acute inflammation, such as pediatric elective abdominal surgery. Some literature states that this parameter is more optimal as a predictor of outcome in

severe inflammatory conditions or critical illness than as a differentiator of the effectiveness of analgesic techniques. Therefore, the absence of significant differences between NLR and PLR between groups in this study needs to be interpreted carefully (Gao et al., 2021).

Fourth, pain assessment using NRS, although valid for children aged ≥6 years, still has an element of subjectivity and is influenced by psychological and environmental factors. Differences in pain perception between individual children and parental involvement in the assessment process have the potential to cause reporting bias (Tsze et al., 2018) .

Taking these limitations into account, the results of this study still make a meaningful contribution to understanding the comparative effects of *continuous fentanyl* and *epidural levobupivacaine* on pain and inflammatory response in pediatrics, and may serve as a basis for further research with multicenter designs, larger sample sizes, and more comprehensive biomarker evaluations.

CONCLUSION

Based on the results of the research and discussion presented, it can be concluded that:There was no difference between continuous fentanyl administration and epidural levobupivacaine in postoperative interleukin-6 (IL-6) levels in pediatric patients undergoing laparotomy, There was no difference between continuous fentanyl administration and epidural levobupivacaine in postoperative changes in the neutrophil-to-lymphocyte ratio (NLR) in pediatric patients undergoing laparotomy, There was no difference between continuous fentanyl administration and epidural levobupivacaine in postoperative changes in the platelet-to-lymphocyte ratio (PLR) in pediatric patients undergoing laparotom and There was a significant difference in the reduction of postoperative pain intensity measured using the Numerical Rating Scale (NRS) between continuous intravenous fentanyl administration and epidural levobupivacaine in pediatric patients aged 6–12 years undergoing laparotomy, with greater pain reduction observed in the epidural levobupivacaine group.

REFERENCES

Aliyu, M., Zohora, F. T., Anka, A. U., Ali, K., Maleknia, S., Saffarioun, M., & Azizi, G. (2022). Interleukin-6 cytokine: An overview of the immune regulation, immune dysregulation, and therapeutic approach. International Immunopharmacology, 111, 109130. https://doi.org/10.1016/j.intimp.2022.109130

Bain, C. R., Myles, P. S., Corcoran, T., & Dieleman, J. M. (2023). Postoperative systemic inflammatory dysregulation and corticosteroids: a narrative review. Anaesthesia, 78(3), 356–370. https://doi.org/10.1111/anae.15896

Campos-Pérez, W., Ramírez-Plascencia, L., Pérez-Robles, M., Rivera-Valdés, J. J., Sánchez-Muñoz, P., Pérez-Vargas, L., González-Landeros, D., Cuevas, J. H. M., & Martínez-López, E. (2022). A comparison of opioid-containing anesthesia versus opioid-free anesthesia using the Cortínez-Sepúlveda model on differential cytokine responses in obese patients undergoing gastric bypass surgery: a randomized controlled trial. BMC Anesthesiology, 22(1), 294. https://doi.org/10.1186/s12871-022-01838-8

Egbuta, C., & Mason, K. P. (2021). Current State of Analgesia and Sedation in the Pediatric Intensive Care Unit. Journal of Clinical Medicine, 10(9), 1847. https://doi.org/10.3390/jcm10091847

Erten, E. (2024). Pediatric Surgeons' Approaches to Postoperative Analgesia in Türkiye. Comprehensive Medicine, 45–50. https://doi.org/10.14744/cm.2023.19480

Fang, J., Wu, W., Liu, J., & Zhang, S. (2023). Deep learning–guided postoperative pain assessment in children. Pain, 164(9), 2029–2035. https://doi.org/10.1097/j.pain.0000000000002900

Franz, A. M., Martin, L. D., Liston, D. E., Latham, G. J., Richards, M. J., & Low, D. K. (2021). In Pursuit of an Opioid-Free Pediatric Ambulatory Surgery Center: A Quality Improvement Initiative. Anesthesia & Analgesia, 132(3), 788–797. https://doi.org/10.1213/ANE.0000000000004774

Gao, P., Liu, J., Wang, X., Zhang, P., Jin, Y., Bai, L., & Li, Y. (2021). The association between neutrophil–lymphocyte ratio and poor outcomes following infant cardiac surgery. BMC Cardiovascular Disorders, 21(1), 529. https://doi.org/10.1186/s12872-021-02345-3

Kurniyanta, I. P., Senapathi, T. G. A., Wiratnaya, G. E., Wahyuniari, I. A. I., & Jonathan, J. (2025). Stress-Free Surgery in Caudal Analgesia: A Literature Review. Bali Journal of Anesthesiology, 9(1), 9–13. https://doi.org/10.4103/bjoa.bjoa_249_24

Laila, D. S., Perdana, A., Permatasari, R. K., Kadim, M., Advani, N., Supriyatno, B., Chozie, N. A., & Djer, M. M. (2024). Neutrophil-to-lymphocyte ratio as a predictor of low cardiac output syndrome after open heart surgery in children with congenital heart disease. Narra J, 4(2), e736. https://doi.org/10.52225/narra.v4i2.736

Lavand'homme, P. (2022). Chronic pain after surgery and trauma: current situation and future directions. Acta Anaesthesiologica Belgica, 73(4), 241–247. https://doi.org/10.56126/73.4.27

Lin, E. J., Prost, S., Lin, H. J., Shah, S., & Li, R. (2025). Combined General/Epidural Anesthesia vs. General Anesthesia on Postoperative Cytokines: A Review and Meta-Analysis. Cancers, 17(10). https://doi.org/10.3390/cancers17101667

Liu, C., Fang, C., He, Q., & Xie, L. (2020). The value of interleukin-6 (IL-6) within 6 hours after birth in the prompt diagnosis of early-onset neonatal sepsis. Translational Pediatrics, 9(5), 629–635. https://doi.org/10.21037/tp-20-239

Mankelkilot, S. N., & Berhane, M. (2025). Prevalence, Severity, and Associated Factors of Postoperative Pain among Paediatric Patients Admitted to Paediatric Wards, Jimma University Medical Center, Ethiopia. Ethiopian Journal of Health Sciences, 35(3), 171–178. https://doi.org/10.4314/ejhs.v35i3.4

Martínez-López, E., Campos-Pérez, W., Ramírez-Plascencia, L., Pérez-Robles, M., Rivera-Valdés, J. J., Sánchez-Muñoz, P., Pérez-Vargas, L., González-Landeros, D., & Cuevas, J. H. M. (2022). A comparison of opioid-containing anesthesia versus opioid-free anesthesia using the Cortínez-Sepúlveda model on differential cytokine responses in patients undergoing gastric bypass surgery: a randomized controlled trial. https://doi.org/10.21203/rs.3.rs-1301535/v1

Sim, N. Y. W., Chalkiadis, G. A., Davidson, A. J., & Palmer, G. M. (2024). A systematic review of the prevalence of chronic postsurgical pain in children. Pediatric Anesthesia, 34(8), 701–719. https://doi.org/10.1111/pan.14918

Tsze, D. S., von Baeyer, C. L., Pahalyants, V., & Dayan, P. S. (2018). Validity and Reliability of the Verbal Numerical Rating Scale for Children Aged 4 to 17 Years With Acute Pain. Annals of Emergency Medicine, 71(6), 691-702.e3. https://doi.org/10.1016/j.annemergmed.2017.09.009

Ulrikh, G. E., Zabolotskii, D. V., Aleksandrovich, Y. S., Koryachkin, V. A., Nezabudkin, S. N., & Ulrikh, D. G. (2018). Levobupivacaine for regional blockades in orthopedics and traumatology in children: recent evidence and future directions. Pediatric Traumatology, Orthopaedics and Reconstructive Surgery, 6(4), 77–83. https://doi.org/10.17816/PTORS6477-83

Walters, S. J., Jacques, R. M., Anjos Henriques-Cadby, I. B., Candlish, J., Totton, N., & Xian, M. T. S. (2019). Sample size estimation for randomised controlled trials with repeated

assessment of patient-reported outcomes: what correlation between baseline and follow-up outcomes should we assume? Trials, 20(1), 566. https://doi.org/10.1186/s13063-019-3671-2

Xu, H., Sun, Y., & Zhang, S. (2019). The Relationship Between Neutrophil to Lymphocyte Ratio and Clinical Outcome in Pediatric Patients After Cardiopulmonary Bypass Surgery: A Retrospective Study. Frontiers in Pediatrics, 7. https://doi.org/10.3389/fped.2019.00308

Zahmatkesh, A., Sohouli, M. H., Hosseini, S. M. E., & Rohani, P. (2023). The role of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in the diagnosis and severity of inflammatory bowel disease in children. European Journal of Pediatrics, 182(9), 4263–4270. https://doi.org/10.1007/s00431-023-05110-0

Zieliński, J., Morawska-Kochman, M., & Zatoński, T. (2020). Pain assessment and management in children in the postoperative period: A review of the most commonly used postoperative pain assessment tools, new diagnostic methods and the latest guidelines for postoperative pain therapy in children. Advances in Clinical and Experimental Medicine, 29(3), 365–374. https://doi.org/10.17219/acem/112600