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Comparison of IL-6 and TNF-α Level Measurements in Patients Given Intravenous Ketorolac and Lidocaine in Postoperative Digestive Surgery Patients

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ABSTRACT

Background: Digestive surgery triggers a systemic inflammatory response mediated by pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). This response can lead to postoperative complications such as ileus and delayed healing. Inflammation management involves medications such as lidocaine, which has anti-inflammatory effects, and ketorolac, which is effective in reducing opioid requirements. However, no studies have compared the effectiveness of the two. Objective: Comparing IL-6 and TNF-α levels in post-digestive surgery patients between the lidocaine and ketorolac groups. Research Method: This study was a randomized clinical trial at Dr. Soetomo General Hospital, involving 28 patients. Data were analyzed using SPSS and the Friedman test. Results: IL-6 levels 0 hours postoperatively in the ketorolac group were 8.38 pg/mL and increased to 9.91 pg/mL at 2 hours postoperatively, while in the lidocaine group, IL-6 levels 0 hours postoperatively were 5.40 pg/mL and decreased to 4.59 pg/mL. However, no significant differences were discovered among the two groups at any time point (p=0.587; p=0.215; p=0.098). For TNF-α levels, the ketorolac group showed an increase from 10.60 pg/mL to 12.78 pg/mL, while the lidocaine group increased from 14.57 pg/mL to 16.00 pg/mL. The Mann-Whitney test results also uncovered no significant within between the two groups (p=0.135–0.854). Conclusion: Neither ketorolac nor lidocaine produced significant differences in postoperative IL-6 and TNF-α levels.

KEYWORDS: Digestive Surgery, Pro-Inflammatory Cytokines, IL-6, TNF-α, Intravenous Lidocaine, Ketorolac

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INTRODUCTION

Digestive surgery invariably involves tissue trauma that triggers a systemic inflammatory response. This response is mediated by a complex network of immune signals, particularly inflammatory cytokines, which play a crucial role in regulating the body's defense mechanisms. One such mechanism involves the activation of Pattern Recognition Receptors (PRRs) such as Toll-like Receptors (TLRs) on immune cells. This activation triggers the release of pro-inflammatory cytokines, including Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α), which are commonly utilized as biomarkers for monitoring postoperative progression [1].

Pro-inflammatory cytokines such as IL-6 and TNF-α are key mediators of the acute phase response following surgical trauma. These cytokines stimulate the production of acute-phase proteins in the liver (e.g., C-reactive protein), recruit leukocytes to the site of injury, and modulate immune and metabolic pathways [2]. IL-6 has been extensively studied as a biomarker of postoperative stress and inflammation, and it correlates with the severity of surgical trauma and the risk of complications. TNF-α is released early in the cascade and acts synergistically to intensify the inflammatory response and promote further cytokine production [3].

Digestive surgery often results in significant tissue injury and a systemic inflammatory response. This inflammatory response can contribute to postoperative complications including ileus, pain, delayed healing, and increased length of hospital stay [4]. In digestive surgery, particularly procedures involving bowel manipulation, there is an additional risk of bacterial translocation, which can further exacerbate systemic inflammation and increase the risk of postoperative infectious complications [1]. Current management strategies include pharmacological approaches utilizing medications to prevent an excessive inflammatory reaction, such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Steroids, Probiotics/Prebiotics, and Immunonutrition [5].

Ketorolac is a potent COX-1 and COX-2 inhibitor, with anti-inflammatory action derived from the inhibition of prostaglandin synthesis at both peripheral and central sites. Unlike opioids, ketorolac does not cause respiratory depression or ileus, making it beneficial in the gastrointestinal surgical patient population [6]. In digestive surgery, ketorolac is frequently employed as part of

multimodal analgesia protocols or Enhanced Recovery After Surgery (ERAS) pathways. Its benefits include reduced opioid consumption and related side effects (e.g., nausea, sedation, ileus), enhanced gastrointestinal motility and accelerated return of bowel function, and anti-inflammatory effects that may mitigate the postoperative systemic inflammatory response [7]. Research by Rafiq et al. [7] demonstrated that the use of ketorolac in abdominal surgery reduced morphine requirements and improved patient satisfaction without significantly increasing side effects.

Lidocaine, a widely used local anesthetic and Class 1B antiarrhythmic agent, is garnering increased attention not only for its anesthetic properties but also for its systemic anti-inflammatory effects, particularly in the postoperative setting. Initially utilized for regional anesthesia and management of ventricular arrhythmias, intravenous lidocaine (IVL) is now being explored for its benefits in reducing inflammation and improving recovery outcomes after major surgery, including gastrointestinal procedures. Emerging evidence indicates that lidocaine exerts anti-inflammatory effects through multiple mechanisms. These mechanisms include inhibition of neutrophil priming and adhesion, suppression of proinflammatory cytokines such as IL-6 and TNF-α, and stabilization of cell membranes [8]. The pharmacological profile of lidocaine allows it to modulate the inflammatory cascade without causing immunosuppression, making it an attractive adjunct in perioperative care. As noted in Miller's Anesthesia (9th edition), the systemic effects of lidocaine are increasingly recognized in the context of multimodal analgesia and ERAS protocols, particularly in abdominal surgery [9].

Several studies have been conducted regarding the anti-inflammatory effects of lidocaine. In the study by McCarthy et al., IV lidocaine was shown to reduce postoperative pain, decrease opioid consumption, and shorten the duration of postoperative ileus [10]. A systematic review and meta-analysis by Sun et al. found that patients undergoing abdominal surgery who received perioperative IV lidocaine experienced a significant reduction in postoperative pain scores and improvement in gastrointestinal function [11]. Another study by Kaba et al. observed that lidocaine infusion during and after abdominal surgery was associated with decreased serum levels of inflammatory markers and enhanced return of bowel function [12].

To date, no study has directly compared the magnitude of the anti-inflammatory effects of NSAIDs, specifically ketorolac, and intravenous lidocaine in patients following digestive surgery. Based on this background, the researcher deems it necessary to conduct a study concerning the anti-inflammatory effects of these two drugs, to aid in providing alternative options for postoperative analgesic administration that not only reduce patient pain but also help modulate inflammation in patients, thereby potentially facilitating faster recovery.

CONCEPTUAL FRAMEWORK

Tissue trauma induced by incision, retraction, organ manipulation, and ischemia-reperfusion leads to the release of various endogenous molecules known as damage-associated molecular patterns (DAMPs), such as High Mobility Group Box 1 (HMGB1), extracellular ATP, and heat shock proteins like HSP70. These molecules not only signal cell damage but also act as biological alarms that activate the innate immune system by binding to pattern recognition receptors like toll-like receptor 4 (TLR4) on the surface of immune cells, particularly macrophages and dendritic cells [13,14].

Upon tissue damage, DAMPs specifically bind to receptors such as Toll-Like Receptor 4 (TLR4), subsequently activating a series of signaling pathways. The core of this process is the MyD88-dependent pathway, which leads to the activation of the nuclear factor kappa B (NF-κB) pathway and the Mitogen-Activated Protein Kinase (MAPK) pathway, comprising ERK, JNK, and p38. This cascade is vital in amplifying the transcription of several pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and Interleukin-8 (IL-8), which are essential in orchestrating the immune response to surgical stress [13,15]. Under conditions of high biological stress such as surgery, this inflammation is further exacerbated by inflammasome activation, particularly NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3), which promotes the maturation and secretion of IL-1β through caspase-1 activation. Concurrently, other transcription pathways such as activator protein (AP-1) also contribute to amplifying this inflammatory response.

In conditions characterized by high biological stress, such as surgical procedures, inflammasome activation, particularly the NLRP3 inflammasome, is activated. NLRP3 activation causes the maturation and secretion of IL-1β through caspase-1 activation, thereby exacerbating the inflammatory response. Furthermore, transcription factors such as Activator Protein-1 (AP-1) can contribute to the heightened inflammatory environment [13,14]. Consequently, the synergistic effects of these pathways can lead to a profound inflammatory state that may impede recovery.

In addition to TLR activation, the complement system is also activated, particularly components C3a and C5a, which function as potent anaphylatoxins and chemoattractant. They recruit neutrophils and macrophages to the injury site, increase vascular permeability, and trigger the release of lysozymes and reactive oxygen species (ROS), which exacerbate tissue damage. These activated neutrophils also contribute to the formation of neutrophil extracellular traps (NETs), which, although intended to capture pathogens, can trigger excessive inflammation if uncontrolled [13].

Concurrent with the local and systemic immune response, surgery also triggers activation of the neuroendocrine system. The hypothalamic-pituitary-adrenal (HPA) axis releases corticotropin-releasing hormone (CRH), which stimulates the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary, subsequently promoting cortisol production from the adrenal glands. Cortisol acts as a negative immunomodulator by inhibiting the production of pro-inflammatory cytokines through negative

regulation of NF-κB and the inflammasome. However, in the context of acute and severe stress such as surgery, cortisol may sometimes be insufficient to counterbalance the escalating rate of inflammation [16]. On the other hand, activation of the sympathetic-adrenal-medullary (SAM) system releases catecholamines such as norepinephrine and epinephrine, which act on adrenergic receptors to modulate immune cell activity. This modulation can either potentiate or suppress the inflammatory response depending on the specific context of immune activation [17].

Increased expression of the cyclooxygenase-2 (COX-2) enzyme in inflamed tissues promotes the conversion of arachidonic acid into prostaglandin E2 (PGE2), a lipid mediator that not only causes pain and local vasodilation but also influences the cytokine profile by promoting IL-6 production and prolonging T-helper cell survival [16]. Thus, COX-2 becomes a strategic point often targeted by various nonsteroidal anti-inflammatory pharmacological agents (NSAIDs) such as ketorolac, indomethacin, meloxicam, and celecoxib. These agents work by inhibiting the conversion of arachidonic acid to prostaglandins, thereby reducing pain and systemic inflammation [16,18].

Various monoclonal antibodies have been developed to directly target key cytokines such as TNF-α and IL-6. Infliximab and adalimumab are anti-TNF biological agents used in various severe inflammatory conditions such as Crohn's disease and rheumatoid arthritis. Meanwhile, tocilizumab, sarilumab, and siltuximab are inhibitors of the IL-6 receptor or IL-6 ligand, playing an important role in reducing systemic inflammatory response and postoperative fever [16,18]. Furthermore, lidocaine, generally known as a local anesthetic, also possesses anti-inflammatory effects through sodium channel inhibition and modulation of immune signaling, proven to reduce cytokine levels such as TNF-α in animal models. Dexamethasone, a potent glucocorticoid, works by suppressing the expression of various pro-inflammatory genes including IL-6 and TNF-α, and by inhibiting NF-κB activity and the NLRP3 inflammasome, making it a frequently used adjuvant in the perioperative setting to suppress inflammation [19].

However, this inflammatory response does not occur in isolation. Several host factors also significantly influence the degree and duration of inflammation. Advanced age correlates with low-grade chronic inflammation, which can exacerbate the postoperative response. Sex also exerts hormonal influences on cytokine expression; estrogen, for instance, is known to have complex immunomodulatory effects. Comorbidities such as diabetes mellitus, heart disease, and obesity can also amplify inflammatory pathways through increased numbers of pro-inflammatory immune cells and resistance to cortisol action. The psychological stress accompanying the surgical process has also been shown to worsen inflammation through neuroimmunological pathways, including HPA axis dysfunction and increased catecholamine production [18].

Research Hypotheses

H1: Levels of the inflammatory factor IL-6 will decrease with the administration of ketorolac and lidocaine in patients following digestive surgery.

H2: Levels of the inflammatory factor TNF-α will decrease with the administration of ketorolac and lidocaine in patients following digestive surgery.

METHOD

Research Population

The population for this study consisted of all patients following digestive surgery in the Post-Anesthesia Care Unit (PACU) of Dr. Soetomo Regional General Hospital.

Research Sample

The sample population was the population that met the inclusion and exclusion criteria, with the minimum sample size derived from the minimum sample formula. The research sample comprised all patients following digestive surgery in the PACU of Dr. Soetomo Regional General Hospital who met the inclusion criteria.

Inclusion Criteria

a. Patients aged 18 to 60 years.
b. Patients following digestive surgery admitted to the Recovery Room.
c. Cooperative patients capable of effective communication.
d. The patient's family or the patient provided signed informed consent.

Exclusion Criteria

a. Patients allergic to the medications, including amide-type local anesthetics, ketorolac, paracetamol, and tramadol.
b. Use of other local anesthetics in large quantities.
c. Patients in shock.
d. Patients with acute tachyarrhythmia (rapid AF), or undergoing amiodarone treatment.
e. Patients with bradycardia.
f. Patients with renal impairment, Blood Urea Nitrogen ≥50mg/dL and serum Creatinine >5mg/dL.
g. Patients with hepatic impairment, Serum Glutamic Oxaloacetic Transaminase and Serum Glutamic Pyruvic Transaminase

levels above 500 IU/L.

Sampling Technique

The sample size determination for this study used a σ value of 3, μ1 of 5, and μ2 of 4 building upon earlier work from Castro et al., 2023. With a significance level of 5% and statistical power of 90%, the minimum sample size required for the two groups in this study was determined to be 30 patients.

Operational Definition of Variables

Table 1: Operational Definition of Variables

No	Variable	Definition	Unit	Data Scale
1.	Treatment	Administration of intravenous Lidocaine or Ketorolac to patients	Treatment Patient	Nominal
2.	Interleukin-6	Proinflammatory cytokine produced by various cell types, including T cells, B cells, macrophages, and fibroblasts	pg/ml	Ratio
3.	TNF-α	Key proinflammatory cytokine produced primarily by macrophages	pg/ml	Ratio

Data Analysis

The research results, comprising frequency and percentage values, median, minimum, and maximum, will be presented descriptively using counts and percentages for categorical variables, and median and interquartile range for numerical variables. Statistical analysis will be performed using SPSS version 26. If the data are not normally distributed, the Wilcoxon Mann-Whitney test will be used; if not normal, the Wilcoxon signed-rank test will be used. Results will be considered statistically significant if a p-value <0.05 is obtained with a 95% confidence interval.

RESULT

Subject Characteristics

A total of 30 patients following digestive surgery who met the inclusion criteria were stratified into two groups: the Ketorolac group and the Lidocaine group. However, during ELISA testing of patient blood samples, one blood sample in the intravenous Lidocaine group was damaged and could not be tested, and one sample in the intravenous Ketorolac group was found to have an extreme outlier value and was excluded from data analysis. Consequently, comparisons were made between the Lidocaine group (n = 14) and the Ketorolac group (n = 14). Basic subject characteristics included sex, age, and BMI.

Table 2: Research Subject Characteristics

Variable	Ketorolac (n=14)	Lidocaine (n=14)	p-value
Sex			0.445[a]
Male	9 (64.3%)	7 (50%)	
Female	5 (35.7%)	7 (50%)	
Age (years)	40.5 (29-60)	37.5 (31-54)	0.612[b]
BMI (kg/m²)	22.94 ± 2.68	23.67 ± 7.08	0.722[c]
[a]Chi-square test; [b]Mann-Whitney test; [c]Independent t-test			

The Chi-Square test suggests the distribution of sex among the two groups demonstrated comparable outcomes (p=0.445). The mean age in the Ketorolac group was 40.5 years (range 29-60), while in the Lidocaine group it was 37.5 years (range 31-54); the Mann-Whitney test indicated no significant difference between groups (p=0.612). The mean BMI values between the two groups also showed no significant difference (22.94 ± 2.68 kg/m² vs 23.67 ± 7.08 kg/m²; p=0.722, independent t-test).

Interleukin-6 Levels

IL-6 levels were measured at three time points: before surgery (IL-6 0), 0 hours postoperatively (IL-6 1), and 2 hours postoperatively (IL-6 2). As the data distribution was non-normal, results are presented as median (minimum-maximum range) and analyzed using the Mann-Whitney test between groups and the Friedman test for within-group comparisons.

Table 3: IL-6 Level Examination Results

Variable	Ketorolac (pg/mL)	Lidocaine (pg/mL)	p-value
IL-6 0 (preoperative)	3.96 (2.08-7.84)	4.54 (1.65-9.48)	0.587[a]
IL-6 1 (0 hours postoperative)	8.38 (1.32-31.05)	5.40 (2.40-10.65)	0.215[a]
IL-6 2 (2 hours postoperative)	9.91 (3.22-41.76)	4.59 (2.79-22.98)	0.098[a]
Δ IL-6	0.53 (-9.34-21.87)	1.11 (-6.68-17.38)	0.679[a]
p-value Friedman test	0.109[b]	0.410[b]	
[a]Mann-Whitney test; [b]Friedman test			

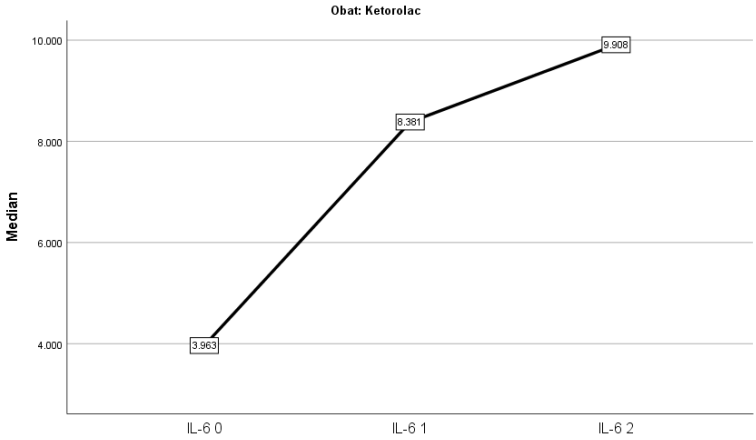

Figure 1: Median IL-6 values before surgery, 0 hours and 2 hours postoperatively in the Ketorolac group

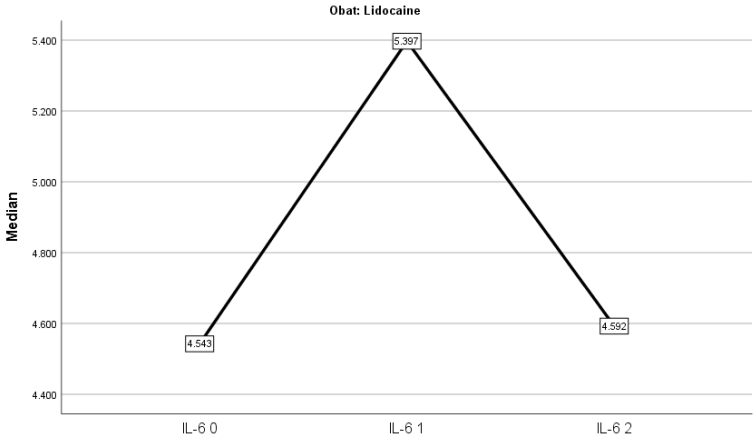

Figure 2: Median IL-6 values before surgery, 0 hours and 2 hours postoperatively in the Lidocaine group

In the Ketorolac group, the median IL-6 level increased from 3.96 pg/mL (2.08-7.84) preoperatively to 8.38 pg/mL (1.32-31.05) at 0 hours postoperatively and 9.91 pg/mL (3.22-41.76) at 2 hours. In the Lidocaine group, the median IL-6 levels were relatively lower: 4.54 pg/mL (1.65-9.48), 5.40 pg/mL (2.40-10.65), and 4.59 pg/mL (2.79-22.98), respectively.
Statistically, no meaningful difference was found in IL-6 levels between the two groups at any time point (p=0.587; p=0.215; and p=0.098, respectively). The Friedman test within each group showed no significant changes in IL-6 levels over time (p=0.109 for ketorolac and p=0.410 for lidocaine).

Tumor Necrosis Factor-α Levels

TNF-α levels were measured at the same time points as IL-6. The data distribution was non-normal, so results are depicted as median (range) and analyzed using the same non-parametric tests.

Table 4: TNF-α Level Examination Results

Variable	Ketorolac (pg/mL)	Lidocaine (pg/mL)	p-value
TNF-α 0 (preoperative)	9.04 (7.63-31.38)	12.88 (9.13-37.99)	0.135[a]
TNF-α 1 (0 hours postoperative)	10.60 (6.95-55.42)	14.57 (8.72-21.13)	0.476[a]
TNF-α 2 (2 hours postoperative)	12.78 (7.46-62.84)	16.00 (7.86-61.30)	0.854[a]
Δ TNF-α	-0.64 (-26.53 - 5.31)	-0.08 (–40.17- 6.53)	0.520[a]
p-value Friedman test	0.319[b]	0.880[b]	
[a]Mann-Whitney test; [b]Friedman test			

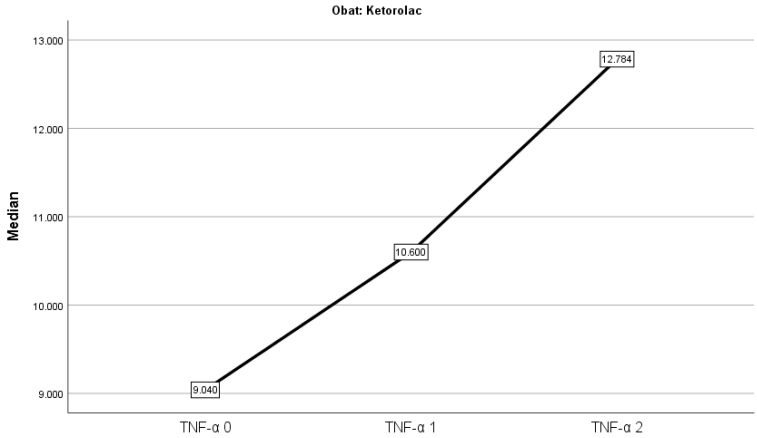

Figure 3: Median TNF-α values before surgery, 0 hours and 2 hours postoperatively in the Ketorolac group

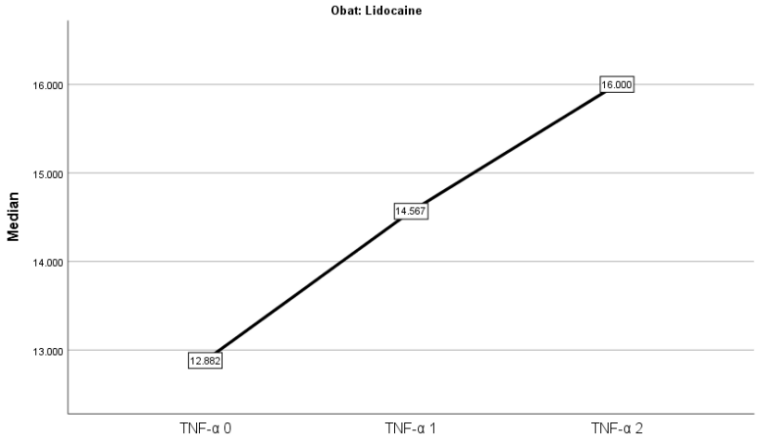

Figure 4: Median TNF-α values before surgery, 0 hours and 2 hours postoperatively in the Lidocaine group

In the Ketorolac group, the median TNF-α level increased gradually from 9.04 pg/mL (7.63-31.38) preoperatively to 10.60 pg/mL (6.95-55.42) and 12.78 pg/mL (7.46-62.84) postoperatively. In the Lidocaine group, the median TNF-α levels were 12.88 pg/mL (9.13-37.99), 14.57 pg/mL (8.72-21.13), and 16.00 pg/mL (7.86-61.30), respectively. The Mann-Whitney test results showed no significant difference between groups at all time points (p=0.135-0.854). The Friedman test also indicated no significant changes in TNF-α levels within each group (p=0.319 for ketorolac and p=0.880 for lidocaine).

DISCUSSION

Research Subject Characteristics

The pattern of basic characteristics in this study aligns with studies by Vigneault et al. and Kim et al., which also reported a predominance of middle-aged male patients in the elective abdominal surgery population. These studies indicated that age and body mass index do not significantly influence postoperative IL-6 levels but may contribute to individual variability in the inflammatory response [20,21].

Compared to the study by Castro et al., which examined the effects of intravenous Lidocaine in colorectal surgery, their subjects' mean age was 45 ± 10 years and BMI 24 ± 3 kg/m², similar to the population in this study. This similarity in characteristics suggests that the data are reasonably representative of the adult digestive surgery patient population in Indonesia and similar international studies [22].

Physiologically, the systemic inflammatory response following surgery is not heavily influenced by sex but tends to be stronger in older patients and those with higher body mass index [4]. As both groups in this study had relatively homogeneous age and BMI distributions, the comparison of cytokine levels between groups can be considered valid without needing correction for demographic covariates.

Following surgery, an increase in IL-6 and TNF-α levels was observed in both groups. The median IL-6 level increased from 3.96 pg/mL (preoperative) to 8.38 pg/mL at 0 hours and 9.91 pg/mL at 2 hours postoperatively in the Ketorolac group. In the Lidocaine group, the median IL-6 level increased from 4.54 pg/mL to 5.40 pg/mL at 0 hours and 4.59 pg/mL at 2 hours. Although this increase

was not statistically significant, this pattern indicates a tendency for a milder increase in IL-6 in the Lidocaine group compared to the Ketorolac group.

Meanwhile, TNF-α levels also increased after surgery. In the Ketorolac group, the median TNF-α level rose from 9.04 pg/mL preoperatively to 10.60 pg/mL at 0 hours and 12.78 pg/mL at 2 hours. In the Lidocaine group, the median TNF-α increased from 12.88 pg/mL to 14.57 pg/mL at 0 hours and 16.00 pg/mL at 2 hours. Although an increase was observed in both groups, no significant difference was found between groups ($p > 0.05$).

Generally, the increase in IL-6 and TNF-α levels postoperatively is a physiological phenomenon resulting from the activation of the inflammatory response to tissue trauma and surgical stress. IL-6 is released by macrophages and endothelial cells within 2-4 hours after tissue injury and often peaks between 24-48 hours [22,23]. TNF-α appears earlier, within the first 1-2 hours, then declines relatively quickly. Therefore, sampling up to 2 hours in this study likely captured only a part of the inflammatory phase, especially for IL-6 which had not yet reached its peak.

Compared to international studies, the pattern of cytokine increase in this study is still similar. A study by Vigneault et al. on abdominal surgery patients reported 2-3 times increase in postoperative IL-6 compared to preoperative values, while TNF-α increased 1.5-2 times within the first 24 hours. Studies by Ortiz et al. and Kim et al. also showed that neither NSAIDs nor Lidocaine infusion completely suppressed the cytokine increase within the first 24 hours but could modulate the speed and intensity of the increase [21,24,25].

The results of this study are consistent with this literature, where both groups showed a pattern of increase in IL-6 and TNF-α that remained within the physiological range of postoperative inflammation, with IL-6 values in the Lidocaine group being slightly lower. This finding is also consistent with a meta-analysis by Cooke et al. which stated that intravenous Lidocaine can significantly reduce IL-6 levels in several studies, but its effect is highly dependent on dose, infusion duration, and type of surgery [26].

From a biological perspective, this supports the notion that Lidocaine has systemic anti-inflammatory effects through inhibition of TLR-4 activation and NF-κB transcription, while Ketorolac works via a different pathway, namely inhibition of COX enzymes and prostaglandin synthesis [8,27]. Although both have anti-inflammatory mechanisms, their influence on systemic cytokines may differ.

Comparison of Interleukin-6 Levels

In this study, the median preoperative IL-6 level (IL-6 0) in the Ketorolac group was 3.96 pg/mL (range 2.08-7.84) while in the Lidocaine group it was 4.54 pg/mL (range 1.65-9.48). There was no significant difference ($p = 0.587$), so the baseline was considered equivalent. Baseline homogeneity is important as it minimizes bias in interpreting the effect of the intervention on IL-6 changes. This aligns with the principle of clinical research that comparison groups must be equivalent in initial characteristics so that changes after intervention can be attributed to the treatment [21].

Literature shows that baseline IL-6 values in surgical populations vary, but relatively low values (e.g., <5 pg/mL) indicate minimal initial inflammatory activation before elective surgery. For example, in the study by Castro et al. on colorectal surgery patients, the mean preoperative IL-6 was 4.8 ± 1.2 pg/mL, a value nearly identical to the data in this study. This similarity strengthens the premise that the population in this study is equivalent to international studies and that confounding factors such as subclinical infection or chronic inflammation before surgery can be relatively ruled out [22].

The study results show a clear numerical trend that the increase in the Lidocaine group was milder than in the Ketorolac group. This pattern is interesting as it suggests that intravenous Lidocaine administration in the surgical setting may limit the rise in IL-6 compared to Ketorolac. This is consistent with meta-analysis findings indicating that perioperative Lidocaine infusion can reduce the IL-6 increase by 20-30% compared to control [26]. For instance, Vigneault et al. reported that Lidocaine infusion in abdominal surgery patients resulted in statistically lower mean postoperative IL-6 compared to control (22 pg/mL vs 30 pg/mL, $p < 0.05$) [21]. Although the design and population differ from this study, a similar direction of findings is observed.

Lidocaine has anti-inflammatory properties through several mechanisms: inhibiting TLR4 activation, suppressing downstream NF-κB, and stabilizing immune cell membranes, thereby reducing cytokine release [20]. In animal and human models, intravenous Lidocaine reduces macrophage activation and production of IL-6 and IL-1β [22]. In contrast, Ketorolac, via COX inhibition, reduces prostaglandin synthesis, but its effect on cytokine production like IL-6 tends to be smaller and more downstream [27]. Therefore, although both drugs have anti-inflammatory effects, Lidocaine's mechanism appears more upstream and could lead to a broader effect on IL-6 expression.

Second, the peak time of IL-6 often occurs at 24-48 hours postoperatively, so sampling up to 2 hours may not have captured the maximum increase in some individuals. Foex and Sear noted that IL-6 can increase up to 10 times at 24-48 hours after major surgery. In this study, the Ketorolac group showed an increase of ~2.5 times from baseline (3.96 → 9.91 pg/mL) within 24 hours, which is relatively low compared to major literature. This could be due to the type of surgery, technique, and the profile of Indonesian patients who may have a different inflammatory burden [28].

Research by Ortiz et al. on major surgery reported that patients receiving Lidocaine infusion experienced an increase in IL-6 from 4.5 pg/mL preoperatively to 7.8 pg/mL at 24 hours (along with reduced opioid requirements) [25]. This study supports that Lidocaine's anti-inflammatory effect is clinically proven. Meanwhile, a study by Kim et al. on laparoscopic surgery concluded no significant difference in IL-6 among the Lidocaine and control groups, but a decreasing trend was still observed (median 6.2 vs 8.1 pg/mL, $p = 0.08$). This work successfully replicates the key finding of Kim study which stated a decreasing trend without statistical significance [24].

A meta-analysis by Cooke et al. discovered that study heterogeneity is considerable, with the IL-6 reducing effect of Lidocaine being more consistent if a dose >1.5 mg/kg/hour is administered for ≥24 hours and in major surgery. In many studies, infusion duration less than 24 hours or variable dosing leads to less consistent effects. This is relevant because in this study, Lidocaine and Ketorolac infusions were given only within the framework of the initial postoperative multimodal analgesia protocol, so the optimal anti-inflammatory effect may not have been achieved [26].

Comparison of Tumor Necrosis Factor-α Levels

This study showed no significant difference between the two groups at all measurement times ($p > 0.05$). Thus, statistically, the effects of both interventions on TNF-α levels can be considered equivalent. Nevertheless, the absolute increase in TNF-α in this study was relatively small compared to reports from other larger studies. For comparison, Castro et al. reported an average increase in TNF-α from 9.7 to 27 pg/mL at 24 hours after colorectal surgery. This suggests that the degree of tissue trauma in this study may have been milder or that both drugs provided a sufficiently strong inflammatory modulatory effect, keeping the TNF-α response within physiological limits [22].

Research by Ortiz et al. showed that patients receiving intravenous Lidocaine infusion during major surgery had lower TNF-α levels compared to control (11.2 ± 4.6 vs 19.8 ± 5.1 pg/mL; $p < 0.05$). This effect was accompanied by reduced opioid requirements and faster recovery of bowel function [25].

Conversely, Kim et al. reported that in laparoscopic cholecystectomy surgery, TNF-α levels did not differ significantly between the Lidocaine and ketorolac groups (12.6 ± 2.8 vs 13.4 ± 3.1 pg/mL; $p = 0.42$), yet the trend of lower values in the Lidocaine group remained consistent. The findings of this study are very similar to that pattern, a biological decrease without statistical significance due to small sample size and short observation duration [24].

In experimental studies, Castro et al. showed that Lidocaine inhibits NF-κB activation and reduces TNF-α production in human macrophage cultures. This effect occurs because Lidocaine stabilizes cell membranes and inhibits TLR4 activation, which normally triggers the MyD88 → IKK → NF-κB signal transduction. Thus, Lidocaine's anti-inflammatory effect is upstream, while Ketorolac acts more downstream through inhibition of COX-1/COX-2 enzymes, which inhibits prostaglandins but does not directly suppress cytokine expression [8,22,27].

Research by Cooke et al. found that Lidocaine consistently reduces IL-6 but does not always affect TNF-α, as the TNF-α peak occurs earlier (≤6 hours). This might also have occurred in this study because sampling was done at 0 hours and 2 hours, so the peak TNF-α phase (2–6 hours) was not fully captured [26].

Anti-inflammatory Mechanisms of Lidocaine and Ketorolac

The evidence from this study implies that neither intravenous lidocaine nor ketorolac administration resulted in a significant difference in IL-6 and TNF-α levels within the first 2 hours postoperatively. Biologically, these findings can be explained by several interacting pharmacological, temporal, and methodological mechanisms.

First, both drugs under investigation possess anti-inflammatory properties, albeit through different pathways. Lidocaine works through central and peripheral mechanisms: inhibiting voltage-gated sodium channels (NaV 1.7 / 1.8), suppressing TLR-4 receptor activation on macrophages, and inhibiting NF-κB translocation into the cell nucleus, thereby reducing the production of proinflammatory cytokines such as IL-6 and TNF-α [20,22]. Meanwhile, ketorolac is a non-selective inhibitor of COX-1 and COX-2 enzymes, reducing the synthesis of prostaglandin E_2 and thromboxane, which also play a role in leukocyte activation and pain sensitization [27]. Although their pharmacological mechanisms are not identical, they share a similar end effect: suppressing mild to moderate systemic inflammatory responses.

Therefore, it is not surprising that the effects of both drugs on reducing IL-6 and TNF-α overlap and ultimately result in equivalent biological responses. This mechanism of "convergence of anti-inflammatory pathways" is often encountered in clinical studies comparing two active anti-inflammatory agents which the effect is not null, but rather the differences cancel each other out because both are effective to a similar capacity [25]. In other words, this study does not show that either drug is ineffective, but that both work almost equally well in suppressing the increase in cytokines after digestive surgery.

Second, physiologically, the release of TNF-α and IL-6 in the postoperative period follows a rapid and dynamic time curve. TNF-α typically peaks within 2-6 hours after surgery, while IL-6 peaks at 24-48 hours [23]. In this study, sampling was performed only at 0 hours and 2 hours. Therefore, it is highly likely that the peak phase of TNF-α was not fully captured, and the peak phase of IL-6 had not yet been fully reached. This condition caused the difference in levels between groups to appear small and not reach statistical significance, although biologically they might have differed if measured more frequently or up to 48 hours. Several other studies that performed serial sampling every 6 hours [21,26] reported that the effect of lidocaine on IL-6 only became clearly apparent at the 36-48 hour point. Thus, the temporal design of this study indirectly became a confounding factor for the actual difference.

Third, the intensity of tissue trauma in this study was relatively uniform and classified as moderate. Elective digestive surgery generally does not produce an extreme systemic inflammatory response like major trauma surgery or sepsis. Under conditions of mild to moderate inflammation, the patient's immune system is still able to maintain a balance between pro- and anti-inflammatory cytokines, leading to high inter-individual variability. In this context, the additional effect of systemic anti-inflammatory drugs is often "buried" within normal physiological fluctuations. Research by Kim et al. showed a similar phenomenon: laparoscopic patients

receiving both lidocaine and ketorolac showed similarly small increases in cytokines without significant difference due to the low degree of surgical stress. In other words, the absence of a significant difference could be because both drugs were working under conditions of already minimal inflammation [24]

The fourth factor is the duration of exposure and drug dosage. The systemic anti-inflammatory effect of lidocaine is known to depend on dose and infusion duration; optimal effects are usually achieved at doses of 1.5-2 mg/kg/hour for ≥24 hours [26]. Ketorolac also has a half-life of 5-6 hours and optimal anti-inflammatory effects within the first 24 hours, but without systemic accumulation. If both drugs are administered for a relatively short period (only a few hours postoperatively), then the effect of systemic cytokine suppression becomes limited. With this short infusion duration, the reduction in IL-6 and TNF-α by lidocaine has not fully developed, while the faster but shorter effect of ketorolac masks the differences between groups. Consequently, at the 2-hour measurement point, the effects of both drugs appear statistically similar.

Fifth, sample size and biological variability also play a role. With a total of 28 patients (14 per group), this study had relatively low statistical power. Based on the high standard variation of IL-6 and TNF-α in the literature (coefficient of variation often > 50%), the number of subjects required to detect a 20% difference between groups is usually more than 40 per group [22]. With a smaller number, biologically real differences often do not reach statistical significance, even if the direction of the effect is clear. This explains why there was a trend of decreasing IL-6 in the lidocaine group ($p = 0.098$) that failed to reach the $p < 0.05$ threshold.

In addition to design and statistical factors, there is a possibility that the molecular mechanisms of the two drugs complement each other in the early inflammatory phase. Ketorolac suppresses prostaglandin production, which plays a role in neutrophil activation and the release of secondary inflammatory mediators, while lidocaine suppresses the TLR-NF-κB pathway that regulates the transcription of IL-6 and TNF-α. If they act in different time domains which ketorolac immediately reduces prostaglandins while lidocaine takes time to reduce cytokine gene expression then the final effect measured at 24 hours could become similar, as both pathways contribute to the same equilibrium point, namely decreased systemic inflammation. Thus, non-significance does not mean absence of effect, but rather biological equivalence of outcomes between two different pathways of inflammation modulation.

Another possible explanation is the presence of endogenous compensatory immune mechanisms. The human immune system maintains a dynamic balance between proinflammatory (TNF-α, IL-6) and anti-inflammatory (IL-10, TGF-β) cytokines. Excessive suppression of one pathway is often balanced by an increase in opposing cytokines to maintain homeostasis [4]. Therefore, although lidocaine suppresses IL-6 production, the body may increase the release of other mediators to maintain inflammatory balance. Ketorolac also induces similar modulation through its analgesic effect and pain reduction, which suppresses sympathetic activation. Consequently, the final cytokine profile of both groups becomes similar even though the underlying mechanisms differ.

Patient factors also have an influence. The perioperative inflammatory response is influenced by age, sex, nutritional status, and metabolic condition. In this study, both groups had homogeneous BMI and age ranges, but genetic variation in the expression of TLR4 or COX receptors could cause large individual differences [29]. In the context of a small sample, such genetic variability reduces the chance of detecting differences between groups.

It must be emphasized that statistical non-significance does not always equate to clinical non-significance. Although the p-value did not reach < 0.05, the direction of the difference showed a consistent biological trend: IL-6 and TNF-α levels in the lidocaine group were slightly lower than in the ketorolac group. This indicates that lidocaine does indeed have a systemic anti-inflammatory effect, but to a degree similar to ketorolac. Practically, this result actually strengthens the premise that both drugs can be used equivalently in perioperative multimodal analgesia protocols to suppress mild to moderate systemic inflammatory responses.

Study Limitations

This study has several limitations that need to be considered when interpreting the results. First, due to equipment limitations, namely monitors for postoperative care in the inpatient ward, patient observation could only be conducted in the Recovery Room, as intravenous lidocaine administration requires monitoring, thus observation was limited to 2 hours.

Second, the sampling time was limited to 0 hours and 2 hours postoperatively. However, TNF-α typically peaks within 2-6 hours and IL-6 within 24-48 hours after major surgery. Consequently, the kinetic pattern of cytokines was not fully depicted, and differences between groups may not have been optimally captured.

Third, the duration of administration and drug dosage were not designed to achieve maximal anti-inflammatory effects. The lidocaine infusion was given only during the 2-hour postoperative period in the Recovery Room, while other studies show optimal anti-inflammatory effects occur at doses ≥ 1.5 mg/kg/hour for ≥ 24 hours.

Fourth, this study did not assess the correlation wihtin cytokine levels and clinical parameters such as pain intensity, length of stay, or postoperative complications, so the clinical significance of cytokine changes could not be determined comprehensively.

Thus, the results of this study should be considered exploratory findings depicting biological trends, and further research with longer observation periods, more standardized dosing, and measurement of other variables that can add clinical meaning to cytokine changes is needed to confirm the clinical significance of the effects of lidocaine and ketorolac on the postoperative inflammatory response.

CONCLUSION

Based on the analysis of 28 elective digestive surgery patients who were randomly assigned to two treatment groups, the findings indicate that there was no significant difference in IL-6 or TNF-α levels between the Lidocaine and Ketorolac groups at any measurement point. Further research with extended blood sampling intervals of up to 48-72 hours and standardized dosing is needed to more accurately capture cytokine dynamics and to clarify their relationship with clinical parameters such as pain intensity, length of hospital stays, and postoperative complications, thereby enabling a clearer evaluation of the clinical relevance of anti-inflammatory effects. Subsequent studies should also correlate cytokine levels with objective clinical indicators, including pain scores (VAS or NRS), opioid consumption, length of stay, time to recovery of bowel function, and complication rates, as these associations would offer stronger translational insight into the role of lidocaine as a perioperative anti-inflammatory agent. In addition, future work should incorporate other biomarkers such as IL-10, CRP, and cortisol to develop a more comprehensive understanding of inflammatory balance and metabolic stress in the perioperative period.

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