Original Article

Effects of Anesthetic Management on Inflammatory Markers in Patients After Major Abdominal Surgeries: A Double-Blind Controlled Study

Esam Hamed[1], Nagla El-Melegy[2], Samir Ammar[3], Rasha Hamed[1*]

Abstract

Background: Surgical trauma induces systemic inflammatory responses. We aimed to evaluate the influence of different analgesic models on postoperative pain and inflammatory markers modulation after major abdominal surgeries.

Materials and Methods: A total of 105 patients scheduled for elective abdominal colorectal surgeries were selected and randomly assigned to one of the three groups: Group-1 (GM) four micrograms/kg of IT morphine; Group-2 (GML) four microgram/kg of IT morphine plus 1.5 mg/kg intravenous Lidocaine loading dose and 2 mg/min saline infusion during the operation and the next 4 hours postoperative; Group-3 (G0, control group) no added drugs.

Results: Pain scored statistically significant lower figures in GML than the other two groups; p<0.001. Tumor Necrosis Factor-alpha serum levels showed a statistically significant difference between the three groups; P <0.001; GML showed the lowest level, followed by group GM and Group 0 (10.3±4.4 vs. 20±4.4 vs. 26±7.5). Transforming Growth Factor beta-1 demonstrated the highest levels measured in GML, high levels in GM, and the lowest level in G0; p<0.001, where mean serum levels were 43.1±12.5, 26 ±4.2, and 18.9±7.7, respectively. Opioid consumption was significantly lower in GML than other two groups; P<0.001.

Conclusion: Intraoperative and early postoperative intravenous Lidocaine infusion significantly improved the quality of postoperative analgesia. Optimizing analgesia in anesthetic management has a favorable effect on the pro and anti-inflammatory mediators.

Keywords: Abdominal surgeries, Postoperative pain, TNF-alpha and TGF-beta

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Introduction

Surgical trauma induces systemic inflammatory response due to hormonal, immunological, and metabolic mediators. It is associated with augmented secretion of various stress hormones such as adrenaline, cortisol, glucagon, growth hormone, aldosterone, and antidiuretic hormones (1). The exaggerated inflammatory response to injury may precipitate a severe systemic inflammatory response syndrome (SIRS) with organ dysfunction (2). Regional and propofol-based anesthesia reduce surgical stress

and perioperative immunosuppression (3).

Most anesthetics relatively modify hypothalamic pituitary adrenal (HPA) axis activity; Etomidate has a well-known inhibitory effect on the HPA axis, ketamine has a lesser influence on HPA function, propofol has a suppression effect on the HPA axis in vitro, but with unclear clinical impact. Opioids and local anesthetics can suppress the HPA axis function, perhaps due to their analgesic effect suppressing stress hormone production (4).

Transforming Growth Factor-beta is a family of cytokines with three isomers (TGF- β 1, 2, and 3) that play an essential role in regulating and developing growth. (5). It exerts primary regulatory effects on nociceptive transmission. It provides protective effects against neuropathic pain following nerve injury. The possible mechanism is glial activation inhibition, inflammatory cytokine release prevention, and protection against neuronal apoptosis in the spinal cord (6).

Tumor Necrosis Factor-alpha (TNF-α) is a primary inflammatory mediator responsible for many physiological changes such as fever, hypotension, tachycardia, and changes in consciousness. It has an antigenic activity by stimulating the release of prostaglandins, interleukin (IL-6), IL-8, and tissue factor III from monocytes and endothelial cells, which might play a role in disseminated intravascular coagulation. Overproduction of TNF could harm the host, as seen in pathologies such as cachexia, autoimmune disorders, and septic shock (7).

Surgery variably affects both pro-and anti-inflammatory systems. Lidocaine infusion could favorably modify surgery-induced pro-inflammatory effects; it probably blocks the induced activation of polymorphonuclear leukocytes (PMNs), leading to the release of cytokines and Reactive Oxygen Species (ROS). This effect occurs when the cells are exposed to low lidocaine concentration for a prolonged period (hours), perhaps mediated by inhibiting a specific intracellular G-protein signaling molecule (8). To our knowledge, this is the first study to examine the effect of lidocaine infusion as an anesthetic adjuvant on TGF-β and TNF-α release in patients undergoing abdominal surgeries.

We hypothesize that adding lidocaine infusion intra and early postoperative as an adjuvant to anesthesia technique can improve pain parameters, positively affect the pro and anti-inflammatory markers, and optimize postoperative analgesia.

Methods

This study was a randomized, double-blind controlled clinical trial (RCT). Carried out at Assiut University Hospital after approval of the ethics committee Board (Number:17300478) and registered on the Clinical trial registration website (NCT04630938). Patients scheduled for abdominal colorectal surgeries were provided with a detailed description of the study and the possible benefits and risks before consenting to participate. The study was in line with the Helsinki Declaration and STROBE guidelines.

The primary outcome measures were the plasma levels of TNF-α and TGF-β1 after the recovery from the operations. The secondary outcome measures were postoperative pain parameters, backup analgesic requirements, and side effects of the technique.

Preoperative assessment: All patients were evaluated for eligibility, and preoperative laboratory workups consisted of complete blood picture (CBC), electrocardiography (ECG), serum blood urea and creatinine, prothrombin time, and concentration erythrocyte sedimentation rate, and C-reactive protein levels were conducted. All participants were monitored in our high-dependence post-anesthesia care unit during the study time (24 hours).

Inclusion criteria: Adult patients aged 18 - 80 years old, Patients scheduled for abdominal surgeries and are not in an acute inflammatory status, Patients with American Society of Anesthesiologists (ASA) I, II physical status

Exclusion criteria: Patients' refusal, Presence of overt inflammatory conditions, critically ill patients, and Patients who have contraindications to regional anesthesia.

Sample Size Calculation: The sample size was calculated using G*Power 3 software as described in a previous study (9). The program was fed a power of 80% and a type I error of 5% (α=0.05 and β=80%) on the two-tailed test. The minimum required sample was 81 participants divided into three equal groups; 27 patients were needed for each group to detect an effect size of 30% in the mean TGF-β/TNF-α between the

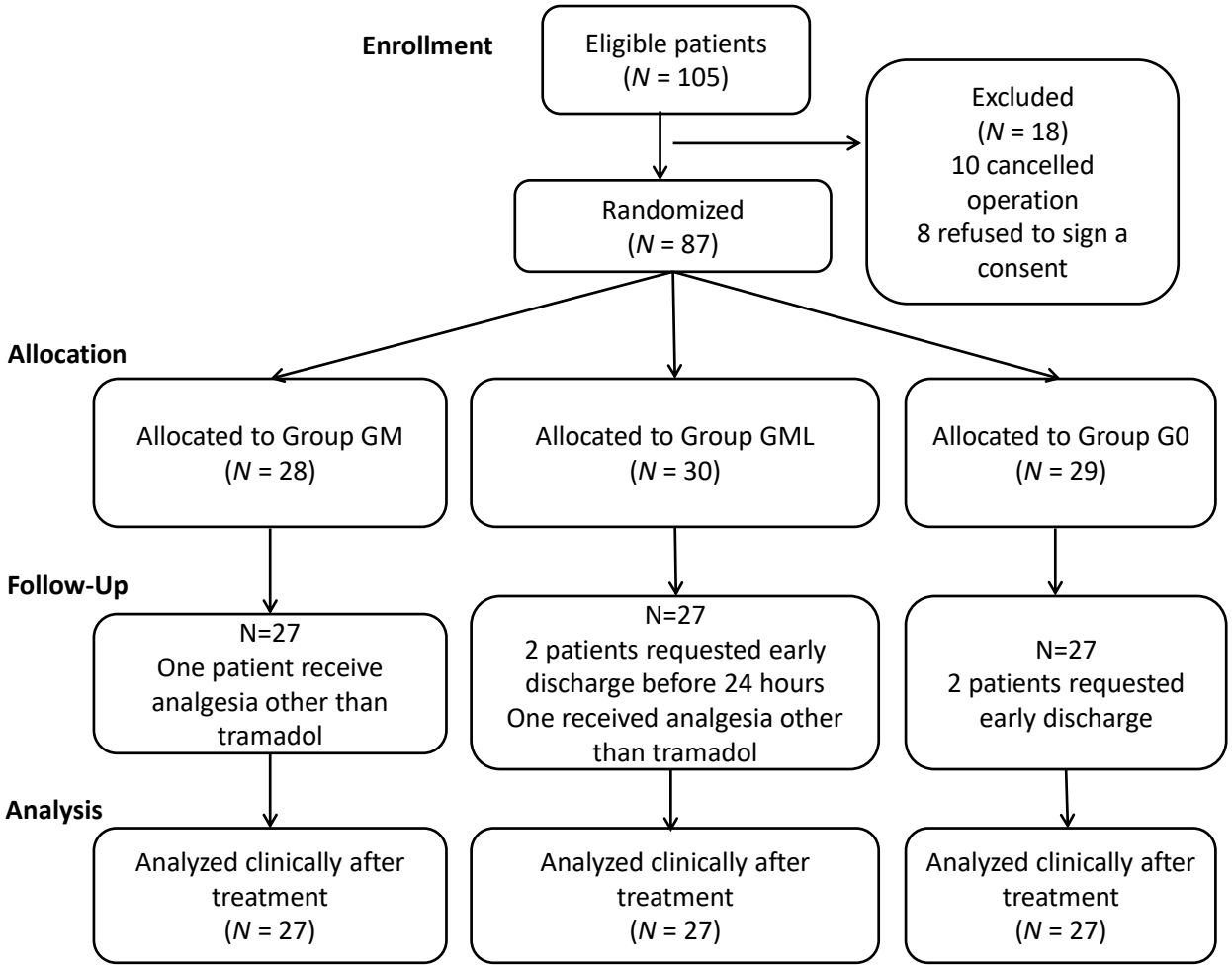

Figure 1. flow chart.

three studied groups (9).

Randomization: All recruited patients who fulfilled the study's inclusion criteria sequentially received the same anesthesia technique in spinal anesthesia (SA) with heavy Bupivacaine 0.5% (3 ml) given at an appropriate spinal level of their back using a 27G pencil tip spinal needle. After stabilizing the spinal level of the block at the 7th dorsal spine dermatome, general anesthesia was initiated utilizing a propofol sleeping dose (1.5-2.5 mg/kg) and Cisatracurium 0.15 mg/kg. Control the patient's airway after endotracheal intubation and controlled mechanical ventilation. After securing the airway, an orogastric tube was inserted to decompress the stomach in all patients. Isoflurane Anesthesia 0.5–1 Minimum Alveolar Concentration (MAC) is used during the operation to maintain Anesthesia.

All patients received an infusion of either saline or Lidocaine prepared explicitly at our local research pharmacy and sent to the operating theatre labeled with the study group and the infusion rate. Patients were assigned randomly according to a performed computer-generated random table into one of three groups:

- **Group-1 (GM):** Received IT Bupivacaine 15 mg and Morphine four microgram/kg, classic general anesthesia, and saline infusion intraoperative and 4 hours postoperative.
- **Group-2 (GML):** Received IT Bupivacaine 15 mg and Morphine four microgram/kg, classic general Anesthesia, and Lidocaine in a loading dose of 1.5 mg/kg then 2 mg/min with the saline infusion along the time of the operation plus the next 4 hours postoperative.
- **Group-3 (GC):** Received IT Bupivacaine 15 mg, classic general anesthesia, and saline infusion intraoperative and 4 hours postoperative.

The anesthesiologist was blinded, and another

investigator not involved in the patient care managed the drug preparation, delivery, and blinding technique. Standard ASA monitoring measures were applied to all patients during the intraoperative time. Tramadol was available for rescue postoperative analgesia in a dose of 50 mg intravenous four-hourly as per the patients' request, with a maximum dose of 400 mg/24 hours. All patients were monitored postoperatively for pain scores, total dose requirements of the rescue analgesia, hemodynamic parameters, and incidence of side effects.

Laboratory work: Levels of pro-inflammatory mediator TNF-α and anti-inflammatory mediator cytokine TGF-β1 were measured in all patients after four hours of recovery from anesthesia. Five ml of venous blood under complete aseptic conditions was collected. The blood samples were allowed to clot at room temperature for one hour and then centrifuged at 3000 revolutions per minute (rpm) for 10 minutes. The serum was separated, divided into aliquots then stored at –20 ^{0}C for analysis afterward. Quantitative determination of serum TNF-α was estimated using AviBion human TNF-α ELISA kit (Catalog No; TNFa021) supplied by Orgenium Lab., Helsinki, Finland, to the method of Leros-Roels (10). Serum levels of TGF-ß1 were measured using an ELISA kit (Catalog No; EIA 1864) supplied by DRG Instruments, GmbH, German (10).

Statistical analysis: IBM Statistical package for the social sciences (SPSS) version 22 Inc., Chicago, IL, USA program was used to perform all the statistical analyses of this study. For normality, the Shapiro-Wilk test was used to manage the data. To analyze categorical data, the Chi-square test was used. The parametric data type was collected using variance analysis (ANOVA). Post hoc Bonferroni was used to correct for multiple comparisons. Nonparametric data analyzed by Kruskal Wallis test for analysis of the variance with multiple pairwise comparisons. A p-value of <0.05 was considered statistically significant.

Results

Out of 105 patients who fulfilled the inclusion and exclusion criteria, 81 patients completed the study; 27 in group-1 (GM), 27 in group-2 (GML), and 27 patients in control group-3 (GC) (Fig. 1). No statistical differences were detected in the demographic data (age, sex, and weight) among the three groups, as shown in (Table 1).

All Patients demonstrated stable hemodynamic parameters along the intraoperative course and among the three groups of the study. Also, there was a statistically significant difference in TNF-α serum levels among the three groups with *P*<0.001. GML showed the lowest level, followed by group GM and GC (10.3 ± 4.4 vs. 20 ± 4.4 vs. 26 ± 7.5, respectively), where P1 <0.001, P2=0.001, and P3<0.001,

Table 1: Demographic data of the patients who completed the study.

Group (N)	**GM (**27)	**GML (**27)	**GC (**27)	***P*-value**
Age (Mean ± SD)	65 ± 6	64.5 ±6.6	63 ±8.6	= 0.286*
Gender M/F	14/13	12/15	13/14	= 0.442**
Weight (Mean ± SD) kg	72 ± 6	70 ±6	71 ±7	= 0.601*

**P= Analysis of the variance via one-way ANOVA among the three groups*
***P*= Chi ^{2} *test*

Table 2: The comparison of the serum levels of TNF-α and TGF-β1 in study groups.

	Group M	**Group ML**	**Group 0**	**P1**	**P2**	**P3**	**P**
TNF-α	20 ± 4.4	10.3 ± 4.4	26 ± 7.5	<0.001	0.001	<0.001	<0.0001
TGF-β1	26 ± 4.2	43.1 ± 12.5	18.9 ± 7.7	<0.001	0.01	<0.001	<0.0001

P1= comparison between groups 1 and 2, P2= comparison between groups 1 and 3, P3= comparison between group 2 and 3, P= Analysis of the variance via one-way ANOVA among the three groups (prepared using SPSS version 22 Inc., Chicago, IL, USA)

Table 3: Comparison between Pain Parameters (VNRS) in study groups along with the 24-hours of the study.

	Group M	Group ML	Group 0	*P1*	*P2*	*P3*	*P*
VNRS H-1	0.00	0.07±0.3	2±0.9	0.7	<0.001	<0.001	<0.001
VNRS H-2	0.74±0.45	0.07±0.3	2.6±1.1	0.001	<0.001	<0.001	<0.001
VNRS H-3	1±0.7	0.5±0.6	3.8±1.9	0.06	<0.001	<0.001	<0.001
VNRS H-4	1.74±0.45	1±0.6	2.8±1	0.001	<0.001	0.002	<0.001
VNRS 1-4	0.9±0.4	0.42±0.4	2.8±1	0.15	<0.001	<0.001	<0.001
MVNRS 4-8	2 ±0.7	1.6±0.6	4.4±1	0.2	<0.001	<0.001	<0.001
MVNRS 8-12	2.74±0.45	2±1	4.7±1.2	0.03	<0.001	<0.001	<0.001
MVNRS 12-16	2.78±0.8	2±0.7	6±1.4	0.03	<0.001	<0.001	<0.001
MVNRS 16-20	3.78±0.6	2.2±0.4	5±1.3	<0.001	0.01	<0.001	<0.001
MVNRS 20-24	3±0.7	2.7±0.7	5.7±1.3	0.2	<0.001	<0.001	<0.001

respectively, as shown in Fig. 2 and Table 2. The level of TGF-β1 was significantly higher in GML (43.1 ±12.5 ng/ml) compared with GM (26 ± 4.2 ng/ml, p=0.01) and GC (18.9 ± 7.7 ng/ml, p<0.001). The level of TGF-β1 was also significantly higher in GM compared with GC (Fig. 3 and Table 2**)**.

The pain intensity was measured using the Visual Numeric Rating Scale (VNRS) hourly across the 24 hours of the postoperative period of the study. The assessment was applied on four hourly means at 1-4, 4-8, 8-12, 12-16, 16-20, and 20-24 hours. GM demonstrated low pain parameters along the recording times that were statistically significant (*P*<0.05) in comparison to GC (Fig. 4 and Table-3). At the same time, GML exhibited the lowest pain parameters compared to GM and GC (control group) (*P*<0.05) (Fig. 4 and Table-3). Also, no difference was observed between GM and GML at 1st (1-4 hours), 2nd (4-8 hours), and last intervals (20-24 hours).

The total 24 hours dose of Tramadol as a consumed rescue medicine was low in GM and lowest in GML compared to the control group (GC). This difference was statistically significant (p<0.001). Tramadol consumption was significantly lower in GM than GC (p=0.031), while it was lower in GML than GM (p<0.001) and GC (p<0.001), as shown in Figure 5.

Discussion

The present study revealed that IV Lidocaine infusion as an adjuvant to the anesthetic management protocol employed in this study was associated with a superior and statistically significant analgesia, reduced analgesic requirement, increased production of anti-inflammatory cytokine TGF-β1 and mitigated pro-inflammatory cytokine TNF-α in the postoperative period in patients undergoing elective abdominal colorectal surgeries.

Postoperative pain may result from a combination of inflammatory and neuropathic factors, manifesting as increased pain sensitivity. These two factors are the objectives of intravenous Lidocaine, which proved to be a safe and effective alternative to epidural analgesia to improve perioperative outcomes (11). Thus, it is implicated in enhanced recovery

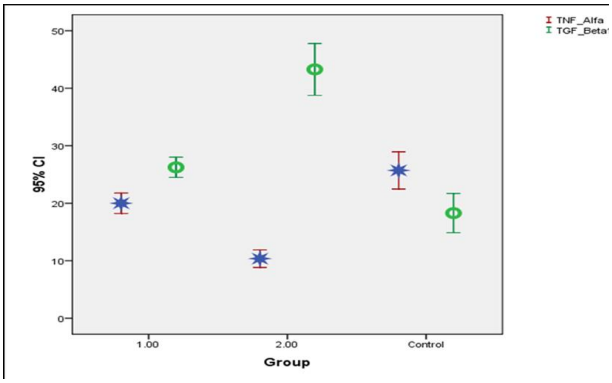

Figure 2. 95% confidence interval of TNF-α and TGF-β1 among the two study groups versus the control group. CI= Confidence Interval, TNF-α = Tumor Necrosis Factor Alpha, TGF –β1= Transforming Growth Factor Beta-1 (1=GM, 2=GML, control=G0) (prepared using SPSS version 22 Inc., Chicago, IL, USA).

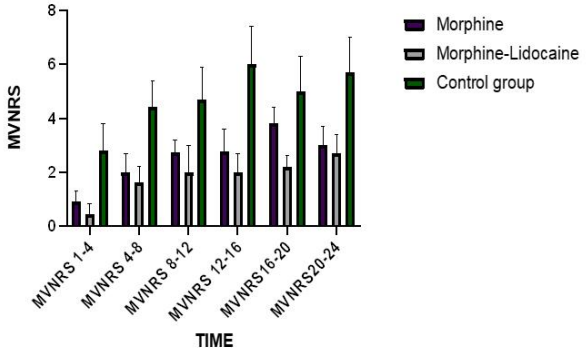

Figure 3. MVNRS between study groups

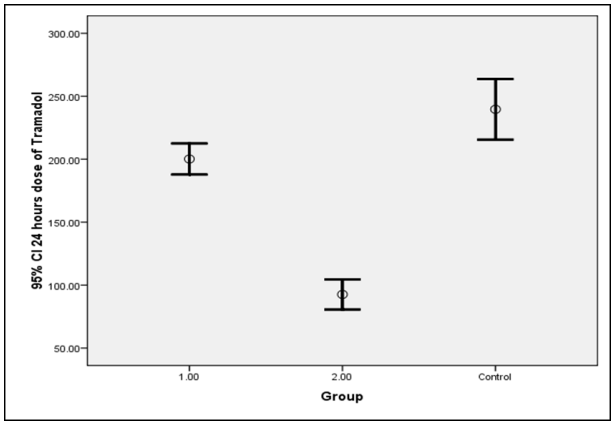

Figure 4. Graphic representation of 95% of confidence interval (CI) of 24 hours dose of Tramadol among the two study groups versus control group *(1=GM, 2=GML, control=GC).*

programs due to its efficacy in alleviating postoperative pain, enhancing gastrointestinal motility, reducing opioid consumption, and opioid-related side effects such as postoperative nausea and vomiting (PONV) (11). Besides its antimetastatic properties, especially in colorectal malignancies (12).

Intravenous Lidocaine has analgesic, anti-hyperalgesia, and anti-inflammatory properties (13). Lidocaine can attenuate postoperative inflammatory response by several mechanisms, attenuating neurogenic inflammation by blocking neural transmission at the site of tissue injury. Furthermore, Lidocaine possesses anti-inflammatory properties and might inhibit granulocyte migration and lysosomal enzyme release, consequently reducing pro-inflammatory cytokines release. Pro-inflammatory cytokines could precipitate peripheral and central sensitization, causing hyperalgesia (13). TGF is a family of cytokines that regulates nociceptive transmission in a pleiotropic manner (14). Especially, TGF-β1 is a vital mediator that protects against neuropathic pain after neuronal injury by inhibiting glial activation, inflammatory cytokine release, and protection against spinal cord neuronal apoptosis (15). In the peripheral nervous system, TGF-1 reduces T-lymphocyte and cytokine/chemokine-secreting macrophage infiltration (16). The literature on Lidocaine infusion in Vivo's effect on postoperative immune response alteration, particularly the TGF cytokine family, is lacking. TGF-β is an extracellular protein secreted by a subset of T-cells but expressed by all cells. Platelets, macrophages, neutrophils, and bone are other significant sources of TGF- β. In mammals, three isoforms of TGF-β are identified (TGF-β 1–3) (17). TGF-β controls cellular replication, progression, and migration. Likewise, it promotes collagen, fibronectin, proteoglycans, tenascins, and thrombospondin synthesis; these processes are crucial in tissue development and wound healing (6). TGF-b is considered a neuroprotection protein; it stimulates the synthesis of nerve growth factors and prevents the in vitro degradation of cultured neurons (18). In animal studies, TGF-β showed promising results in preventing allodynia and improving the analgesic quality of exogenous and endogenous opioid agonists by modulating the presynaptic and postsynaptic endogenous opioid system (6, 19).

Yardeni et al. found that preoperative and intraoperative IV Lidocaine improved immediate postoperative pain and decreased the surgery-induced immune response in patients who underwent a transabdominal hysterectomy. They attributed their

results to the significant reduction in IL-1ra and IL-6 production in the group receiving Lidocaine infusion (13).

Wang et al. detected that intraoperative systemic administration of Lidocaine exerted a protective effect on cell-mediated immunity in cervical cancer patients undergoing radical hysterectomy. Lidocaine in their study elicited a protective effect on lymphocyte function by improving the proliferation rate and attenuating surgery-induced apoptosis of peripheral blood lymphocytes. Moreover, Lidocaine was found to preserve levels of IFN-γ and IL-4, anti-inflammatory cytokines, up to 48 hours postoperative. Finally, Lidocaine decreased the high motility group box-1 protein (HMGB1) levels in the serum, a critical mediator of many inflammatory and noninflammatory diseases and in surgery-associated with sepsis and tumor metastasis. They concluded that these results might be beneficial in reducing the occurrence of postoperative septic complications and tumor metastasis formation (18). Animal studies revealed the beneficial immune-modulatory effect of Lidocaine; Van Der et al. found that Lidocaine infusion increases the plasma and pulmonary IL-10, an anti-inflammatory cytokine, in mechanically ventilated healthy mice (19).

The current study encountered a couple of limitations 1^{st,} the serum level of Lidocaine was not measured, and 2^{nd,} the preoperative levels of the inflammatory markers were not assessed.

Conclusion

Intraoperative and early postoperative intravenous lidocaine infusion significantly improved the quality of postoperative analgesia. Optimizing analgesia in anesthetic management favorably affects the pro and anti-inflammatory mediators.

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