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Effect of Opioid Free Anesthesia versus Opioid-Balanced Anesthesia on Systemic Inflammatory Responses for Elective Oncologic Abdominal Surgeries in Suez Canal University Hospitals: A Comparative Randomized Clinical Trial

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Abstract

Background: Opioids administration consequences are neither scarce nor benign for the patient. The aim of the present study was to improve the systemic inflammatory stress responses and functional outcomes in the patients undergoing elective oncologic abdominal surgery. **Patients and methods:** This prospective clinical trial included 60 patients undergoing elective oncologic abdominal surgery. Patients were equal divided to Opioid Based Anesthesia (OBA) group, and Opioid Free Anesthesia (OFA) group. Each participant was subjected to medical history, physical examination, anesthetic assessments, and laboratory investigations. **Results:** Both groups were well matched as regard sex and age with no statistically significant difference between them. However, the weight of the OFA patients was significantly higher than that of the OBA group. HR and MBP were significantly lower in the OFA group than OBA group at 90 and 120 minutes after induction, at the end of surgery, at extubation, as well as one hour and two hours after surgery. CRP level was significantly lower in the OFA group than in the OBA group at 2 and 24 hours after surgery periods. TLC levels were significantly lower in the OFA group than in the OBA group at 24 hours after surgery. **Conclusion:** OFA is beneficial and effective than OBA. OFA could be recommended in the patients undergoing elective oncologic abdominal surgeries.

Keywords: Elective Oncologic Abdominal Surgeries; Opioids; Inflammatory Responses

Introduction

Opioids are commonly used to supplement sedation during regional anesthesia and as an essential component during induction and maintenance of general anesthesia as well as for treatment of acute post-operative pain. However, administration of opioids can be associated with several side effects that can be responsible for delayed patient recovery and hospital discharge, as well as leading to increased health service costs. Perioperative opioids are associated with nausea and vomiting, sedation, ileus, confusion/delirium, respiratory depression, increased postoperative pain and morphine consumption, immunodepression, and hyperalgesia **(1,2)**.

The strategy of OFA is a realistic alternative that can lead to enhanced recovery and increased patient satisfaction by reducing important opioid related side effects; it can also facilitate the use of lower doses of opioids postoperatively in order to achieve a pain-free recovery and reduce pain scores while providing faster and safer mobilization and rehabilitation **(3)**. The drugs used are hypnotics, N-methyl-D-aspartate (NMDA) antagonists (ketamine, and magnesium sulfate), sodium channel blockers (local anesthetics), anti-inflammatory drugs (non-steroidal anti-inflammatory drugs (NSAIDs) and dexamethasone), and

alpha-2 agonists (dexmedetomidine and clonidine). The association of OFA and loco-regional anesthetic techniques is very common **(4)**.

Several types of patients can benefit from this technique including narcotic history patients, obese patients with obstructive sleep apnea, patients with hyperalgesia and history of chronic pain, immune deficiency individuals, patients undergoing oncologic surgery as well as those affected by inflammatory conditions, chronic obstructive pulmonary disease, and asthma **(5)**. While different OFA protocols have been reported in the literature, the publications rely mostly on case reports and small size investigations **(6)**.

Currently, there has been a move toward opioid-free anesthesia (OFA) to achieve the goals of hypnosis with amnesia and sympathetic stability without the adverse effects of opioids. The first studies on OFA focused on bariatric surgery where respiratory complications are frequent. OFA with dexmedetomidine significantly attenuated postoperative pain and reduced opioid requirements without causing respiratory depression in obese patients. OFA was thereafter proposed for awake neurosurgery, and various minor, or major surgeries. Two meta-analyses have concluded that intraoperative dexmedetomidine reduced postoperative pain and opioid consumption **(7-9)**. One study showed a reduction in postoperative nausea and vomiting **(10)**. However, proofs of the effect of OFA on reducing opioid-related adverse events after major or intermediate non-cardiac surgery are still scarce. Therefore, researchers must design studies with rigorous methodology in order to correctly assess the risks and benefits of OFA for patients in different surgical settings **(8)**.

The systemic inflammatory response to vigorous stimuli as trauma, surgical tissue injury, anesthesia and post-operative pain implies the activation of the sympathetic nervous system, the endocrine response to stress, immunological and hematological changes **(11,12).**

We hypothesized that the OFA technique compared with the standard of care is associated with a reduction of systemic inflammatory stress responses, a decrease of postoperative opioid-related adverse events, in addition to better hemodynamic stability and an enhanced functional outcome in the patients undergoing elective oncologic abdominal surgeries. Therefore, the aim of this study is to assess and compare the effects of opioid free-anesthesia versus opioid-balanced anesthesia on the systemic inflammatory stress responses, functional outcome, hemodynamic stability, reduction of post-operative analgesic consumption and postoperative adverse effects in the patients undergoing elective oncologic abdominal surgery. Therefore, this study aimed to improve the systemic inflammatory stress responses, functional outcome, reduction of post-operative analgesic consumption and postoperative adverse effects in the patients undergoing elective oncologic abdominal surgery as an integrated protocol in enhanced recovery pathway at Suez Canal university hospitals.

Patients and Methods

A prospective randomized single-blinded clinical trial design included **p**atients with American Society of Anesthesiologists (ASA) physical status III or IV undergoing elective oncologic abdominal surgery under general anesthesia. The patients were randomly assigned into one of two equal groups according to a computer-generated randomization list, with a sealed envelope technique:

- Group (I) or Opioid Based Anesthesia (OBA) included patients who received bilateral erector spinae plane block in addition to TIVA by fentanyl as basic analgesic in addition to continuous IV infusion of propofol and varying its rate to keep the spectral entropy in the target range intra-operatively.
- Group (II) or Opioid Free Anesthesia (OFA) included patients who received bilateral erector spinae plane block in addition to TIVA by dexmedetomidine and ketamine,

lidocaine as basic analgesics in addition to continuous IV infusion of propofol and varying its rate to keep the spectral entropy in the target range intra-operatively.

Inclusion criteria:

Patient aged 18-65 years old of both sex. Patients who are ASA III or IV physical status. Patients scheduled for elective oncologic abdominal surgery.

Exclusion criteria:

Patients with known allergy to the study drugs. Patients administered medications known to affect the sympathetic response (sympathetic blockers, benzodiazepines, antiepileptic drugs, alcohol or α2-agonist), glucocorticoid or hormone replacement therapy. Patients with coagulopathy, psychotic disorders, history of severe untreated non-psychotic emotional disorders or cognitive impairment which may interfere with perioperative and follow-up procedures.

Ethical Consideration:

An approval of the study was obtained from Suez Canal University Academic and Ethical Committee. Written informed consent of all the participants was obtained. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Clinical evaluation

Full history and complete clinical examination,and anesthetic assessments were performed including examination of the limbs for prediction of difficult cannulation, airway assessment as thyromental distance, mallampatti score, neck and tempro-mandibular joint mobility, and assessing the absence of deformities in the mandible, face, tongue, palate, teeth and neck that may interfere with airway management. Laboratory investigations such as complete blood count, prothrombin time and partial tissue thromboplastin time, serum creatinine, and urea, Alanine and Aspartate transaminase, and serum bilirubin and random blood sugar, ECG, Chest X ray, Serum ions including sodium, potassium, calcium were done.

Anesthetic Techniques:

Patients had fasted for 6-8 hours. A 18-G size cannula is inserted at peripheral accessible veinPre medication with 0.01 mg/ kg intramuscular atropine was given 3o min before the procedure. Monitoring equipment was connected to closely observe the patients including 5 leads electrocardiogram, non-invasive blood pressure, pulse oximeter, by using Datex-Ohmeda™ monitor, neuromuscular monitor and capnography. The depth of anesthesia DOA was monitored with entropy.

The erector spinea plane block (ESPB) catheters were inserted with the patient awake. The patient was positioned sitting and the skin of the upper back is prepared with 2% chlorhexidine solution. Counting down from the spine of seventh cervical vertebrae, the spine of the ninth thoracic vertebrae (T9) is identified.Once the needle was underneath the anterior fascia of the erector spinae muscle, 10 ml of saline 0.9% was injected.A catheter (Portex; Smiths Medical International Ltd) was inserted into the newly formed space underneath the ES muscle and secured. Bupivacaine (20 ml of 0.25% solution) were injected into each catheter over five minutes prior to induction of general anesthesia. Airway devices and anesthesia machine, syringe pump, ventilator, flow meters and equipment were checked promptly.The deapth of anathesia was monitored with entropy module in (Datex-Ohmeda™

monitor).The target response entropy (RE) and state entropy (SE) were 45-55 for surgical anesthesia.

- **Group I of opioid based anesthesia**:

After pre-oxygenation with 100% oxygen for at least 3 minutes and guided by the neuromuscular monitor, the patients in the OBA group received propofol (2 mg/kg) and fentanyl (2µg/kg) followed by cisatracurium 0.15 mg/kg before tracheal intubation. Then, patients were manually ventilated with 100% oxygen till intubation after full relaxation and with entropy value of around 50 by Macintosh laryngoscope and appropriate size endotracheal tube. After tracheal intubation, patients' lungs were mechanically ventilated with an oxygen-air mix (FiO_2 = 0.3) and $ETCO_2$ was stabilized at 32–35 mmHg. Anesthesia was maintained after induction by continuous IV infusion of propofol (50-150 µg/kg/min), fentanyl (0.03-0.1 µg/kg/min) and cisatracurium 0.03 mg/kg .

An initial high infusion rate to account for redistribution and early surgical stimulation was maintained then titrated to a lower dose according to the target depth of anesthesia and hemodynamics parameters.

- **Group II of opioid free anesthesia**:

Lidocaine loading dose (1mg/kg) then (1.5 mg/kg/h) for maintenance. Dexmedetomidine loading dose 1mcg/kg over 10 Min followed by a maintenance of 0.5 mcg/kg/hr. Ketamine 0.5 mg/kg was given as bolus at the time of induction. Anesthesia was maintained after induction by continuous IV infusion of propofol (50-150 µg/kg/min) and titration of cisatracurium 0.03 mg/kg .

In both groups, bilateral erector spinea plane block were used as previously described. Hemodynamics (mean arterial blood pressure and heart rate) were maintained not to exceed 20% of baseline measures. Hypertension was defined as mean arterial blood pressure ≥100 mmHg for more than 1 minute, in spite of well anesthesia depth; a bolus of 0.5µg/kg fentanyl was administered to the patients. Hypotension was defined as mean arterial blood presure ≤60 mmHg for more than 1 minute and was treated according to the cause of hypotenstion. Bradycardia is defined as a heart rate ≤45 (beat/minute) and was treated with IV atropine sulphate.

After skin closure, propofol, lidocaine, dexmedetomidine and fentanyl were discontinued and the inspired oxygen flow rate was increased to 8 L/min and residual neuromuscular block was reversed using the titration method with neostigmine and atropine IV (2.5 mg: 1 mg ratio). Blood samples were collected at 4 different time points (pre-induction, at end of operation, 2 hours, and 24 hours postoperatively into sterile vacuum EDTA tubes and immediately centrifuged at 15,000 g for 10 minutes; samples were stored at -20 degrees till the time of analysis according to the manufacture guidelines.

The whole technique and anesthetic procedures were performed by the same anesthesiologist to avoid as much as possible the inter-individual skill variations. For postoperative pain, all patients received ketorolac 30 mg intravenously/12 hours and paracetamol infusion 1 gm/6 hours. This regimen was applied in addition to continuous ESPB analgesia. The rescue analgesic regime included slow IV morphine (0.05mg/kg) whenever VAS ≥4 at rest or patient's demand.

Measurements

Total leukocyte count and C-reactive protein serum level in milligram/liter. These inflammatory markers were measured at different four time points (baseline, at the end of operation, 2 hours and 24 hours postoperative). Intraoperative hemodynamics including heart

rate in beats/min and mean arterial blood pressure in mmHg. Time to first analgesic request and 24 hours analgesic consumption Time to first flatus (Time between the end of surgery and the moment when the patient first passes flatus. Time to first defecation at end of surgery. Time to first analgesic request and 24 hours analgesic consumption. The time to first need of rescue analgesic. Total rescue analgesic consumption per patient as described in total dose of morphine used in initial 48 hours postoperatively was also recorded. Time to Post-Anesthetic Care Unit (PACU) discharge readiness. Effect of either technique on ERAS pathway including the time to recovery milestones, length of hospital stay, and the incidence of postoperative complications.

Statistical analysis:

Data collected and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data qualitative represent as number and percentage , quantitative continues group represent by mean ± SD. Differences between quantitative independent multiple by ANOVA. P value was set at <0.05 for significant results &<0.001 for high significant result.

RESULTS

Sixty patients with American Society of Anesthesiologists physical status III or IV undergoing elective oncologic abdominal surgery under general anesthesia were included. Patients were randomly assigned into one of two equal groups **(Figure 1)**.

Both groups were well matched as regard sex and age with no statistical significant difference between them. However, the weight of the OFA patients was significantly higher than that of the OBA group **(Table 1).**

The type of surgery performed in both studied groups. The groups were well matched without any statistically significant difference as regard the type of surgery (p=0.718), the majority of OBA group (46.7%), and in OFA group (36.7%) had gynecological surgery **(Table 2)**.

There were no statistically significant differences between both groups regarding the baseline HR, pre-induction HR, HR 1, 5, 30, and 60 minutes after induction as well as HR 4 hours after surgery. However, The HR was significantly lower in the OFA group than OBA group at 90 and 120 minutes after induction, at the end of surgery, at extubation, as well as one hour and two hours after surgery **(Figure 2)**.

The changes in the mean arterial blood pressure, there were no statistically significant differences between both groups in these periods (baseline, pre-induction, at 1, 5, 30, and 60 minutes after induction). However, the MBP was significantly lower in the OFA group than in the OBA group at 90 and 120 minutes after induction, at end of surgery, at extubation, as well as one, two, and four hours after surgery **(Figure 3)**.

The mean time to post-anesthetic care unit (PACU) discharge was significantly higher in the OFA group (18.10 ± 3.680 min) than in the OBA group (14.53 ± 2.255 min) (p<0.001) **(Table 3).**

There were no statistical significant differences in the mean length of hospital stay and shivering between both groups (p=0.097 and 0.754 respectively). Moreover, the OBA group had a significantly higher incidence of nausea and vomiting, 12 patients (40%) and 8 patients (26.7%), (p<0.001) respectively than in the OFA group where 1 patient (3.3%) had nausea and no patient suffered vomiting. Furthermore, a significantly more patients had urinary

retention and ileus in the OBA group, 4 patients (13.3%) and 5 patients (16.7%) compared to no one patient in the OFA group (p=0.038 and 0.020 respectively). Lastly, 2 patients (6.7%) of the OBA group compared to 6 patients (20.0%) of the OFA group had respiratory depression, without significant difference between both groups (p=0.150) **(Table 4).**

There were no significant differences between both groups regarding to the CRP serum level pre-induction and at the end of operation periods. However, the CRP level was significantly lower in the OFA group than in the OBA group at 2 and 24 hours after surgery periods **(Figure 4)**.

There were no significant differences between both groups regarding the TLC levels at pre-induction, end of operation and 2 hour after surgery periods while it was significantly lower in the OFA group than in the OBA group at 24 hours after surgery **(Figure 5)**.

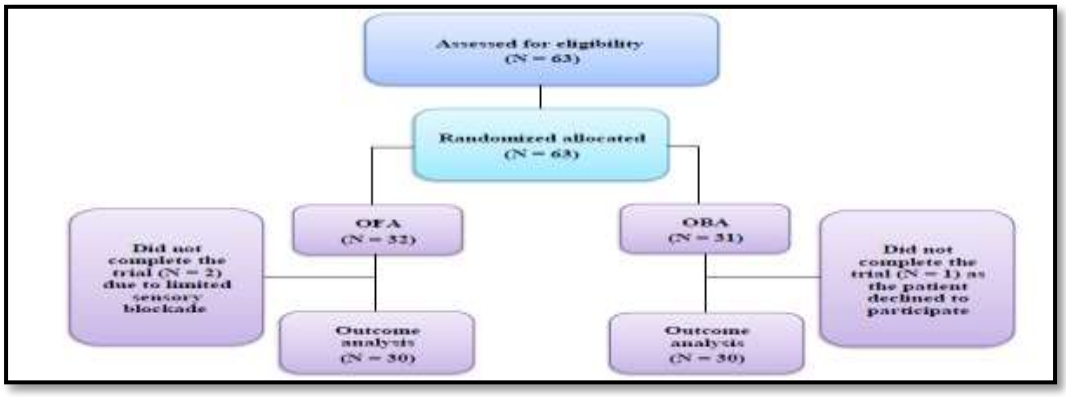

Figure 1: Flow chart of the patients who met the inclusion and exclusion criteria.

Table 1: Demographic data in the two studied groups:

Demographic data	OBA (n = 30)		OFA (n = 30)		Test of Sig.	P
	No.	%	No.	%		
Sex						
Male	21	70.0	20	66.7	χ^2= 0.077	0.781
Female	9	30.0	10	33.3		
Age (years)						
Mean ± SD.	52.30 ± 7.92		52.87 ± 8.08		t= 0.274	0.785
Median (Min. – Max.)	53.50 (40.0 – 70.0)		54.0 (39.0 – 72.0)			
Weight (kg)						
Mean ± SD.	74.93 ± 8.84		81.83 ± 13.44		t= 2.350*	0.023*
Median (Min. – Max.)	75.0 (59.0 – 89.0)		84.50 (59.0 – 105.0)			

*SD: Standard deviation,t: Student t-test,χ^2: Chi square test, p: p value for comparing between the two studied groups, *: Statistically significant at p ≤ 0.05*

Table 2: Type of surgeries performed in both studied groups

Type of Surgery	OBA group (n=30) No. (%)	OFA group (n=30) No. (%)	χ^2	p-value
Gastrointestinal • Cancer cecum (5 patients) • Cancer sigmoid (2 patients)	7 (23.3%)	9 (30.0%)	0.66	0.718
Gynecological • Endometrial carcinoma (9 patients) • Cancer cervix (5 patients)	14 (46.7%)	11 (36.7%)		
Urological • Renal cell carcinoa (4 patients) • Hypernephroma (3 patients) • Cancer bladder (2 patients)	9 (30.0%)	10 (33.3%)		

Non-significant (NS) p-value >0.05

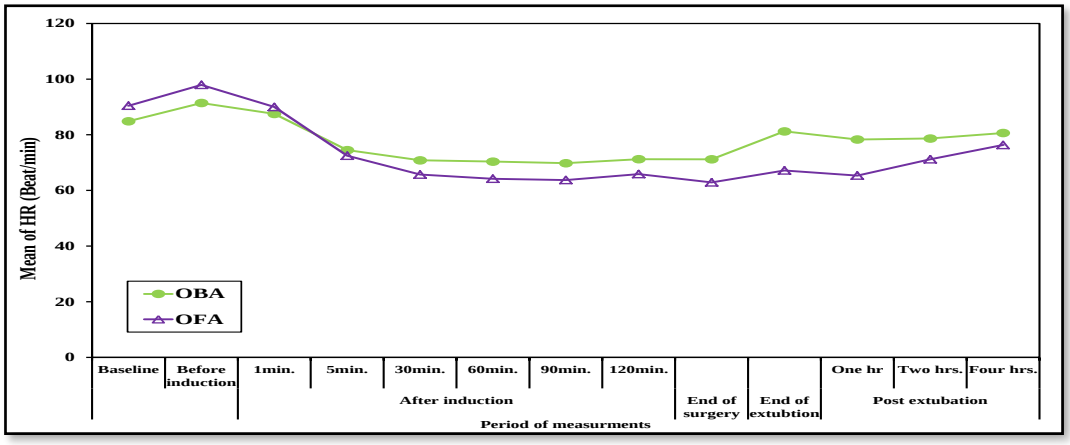

Figure 2: Comparison the heart rate (beat/min) between the two studied groups.

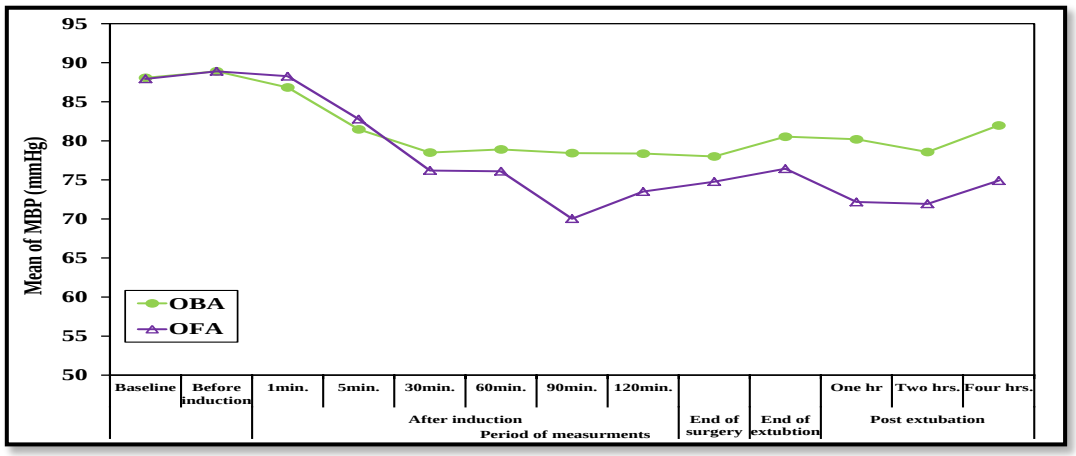

Figure 3: Comparison MBP (mmHg) between the two studied groups.

Table 3: Time to Post-Anesthetic Care Unit discharge in the studied groups

	OBA (n = 30)	OFA (n = 30)	T	P
Time to Post-Anesthetic Care Unit (PACU) discharge (minutes)			4.53	<0.001*
Mean ± SD.	14.53 ± 2.255	18.10 ± 3.680		
Median (Min. – Max.)	14.5 (11-18)	17 (13-25)		

Table 4: Comparison the enhanced recovery after surgery pathway between the studied groups

	OBA (n = 30)	OFA (n = 30)	T/ χ^2	P
Length of hospital stay (days)	4.17 ± 1.859	5.00 ± 1.965	1.69	0.097
Shivering	7 (23.3%)	6 (20.0%)	0.1	0.754
Nausea	12 (40.0%)	0 (0.0%)	15.0	<0.001*
Vomiting	8 (26.7%)	1 (3.3%)	4.7	0.03
Urinary retention	4 (13.3%)	0 (0.0%)	4.3	0.038*
Ileus	5 (16.7%)	0 (0.0%)	5.5	0.020*
Respiratory depression	2 (6.7%)	0 (0.0%)	2.1	0.150

*SD: Standard deviation , t: Student t-test, p: p value comparing between the two studied groups, *: Statistically significant at p ≤ 0.05*

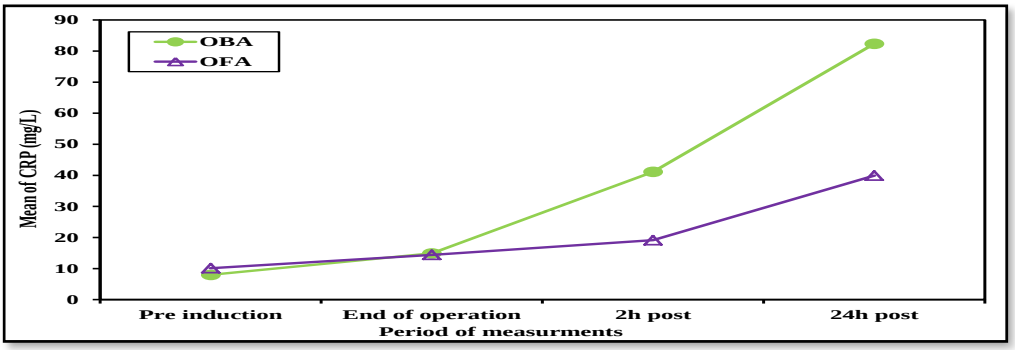

Figure 4:Comparison between the two studied groups according to CRP (mg/L) level.

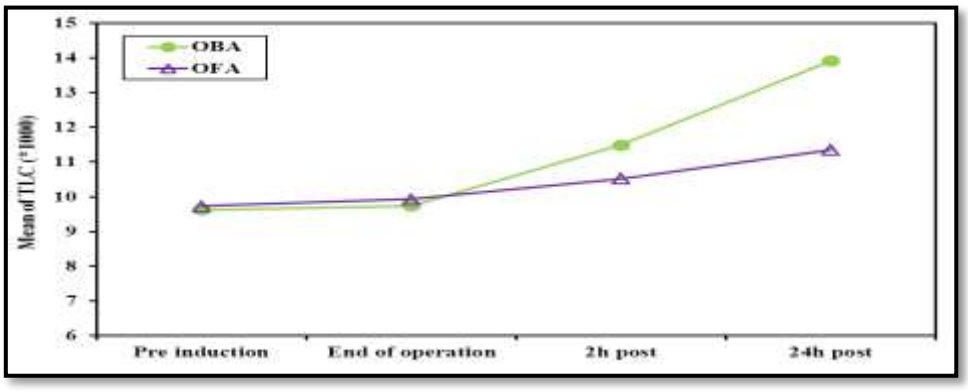

Figure 5: Comparison between the two studied groups according to TLC

DISCUSSION:

It had been shown that by using lidocaine in addition to other analgesics- such as paracetamol, NSAIDS, ketamine, dexmedetomidine and magnesium sulphate, it is possible to provide opioid-free anesthesia in many fields of surgery and it may be important for outcome in cancer surgeries. However, it does not mean that opioids are not needed. It is still debatable and rational approach is needed to avoid "friendly fire" in the anesthetic practice **(13-14)**.

So, this randomized single-blinded clinical trial study was carried out to assess if the opioid free-anesthesia reduce the systemic inflammatory stress responses, reduce postoperative opioid-related adverse effects, possess hemodynamic stability, and enhance functional outcome compared to opioid-balanced anesthesia in the patients undergoing elective oncologic abdominal surgery.

In the current study, both groups were well matched as regard sex and age with no statistically significant difference between them. However, the weight of the OFA patients was significantly higher than that of the OBA group. Therefore, mentioned variables would have minimal influence on the assessed parameters when comparing the two studied groups.

Many inflammatory mediators produced by leucocytes and endothelial cells will elicit pain, which can be counteracted by endogenous opioid peptides in the peripheral nerve terminals **(15)** Inflammatory reactions arise postoperatively leading to activation of pain receptors **(16)**. Regional blocks can elicit complete blockade of impulses reaching the hypothalamus as well as usage of combination of lidocaine infusion, dexmedometedine infusion and ketamine can decreasing the activation of stress response through they anti-inflammatory activity. These effects of stress response include high inflammatory marker and

sympathetic nervous system activation leading to pain, poor functional outcome and altered immune functions.

The results of this study have revealed that there were no statistically significant differences between both groups regarding the baseline HR, pre-induction HR, HR 1, 5, 30, and 60 minutes after induction as well as HR 4 hours after surgery. No clinical difference between baseline heart rate in both group, but in pre induction period HR increased slightly due to anxiety and stress hormones induced by sympathetic nervous system activation , then after induction of anesthesia HR decreed in both group simultaneously due to the myocardial depressant effect of intravenous anesthetics. However, the HR was significantly lower in the OFA group than OBA group at 90 and 120 minutes after induction, at the end of surgery, at extubation, as well as one hour and two hours after surgery , it might be due to the effect of opioid free anesthesia including dexmedotomidine .

Similarly, most previous studies on dexmedetomidine administered intraoperatively during opioid-free anesthesiaor even when administered in the ICU have reported bradycardia **(17,18)**.Also, **Demiri et al. (19)** included 4,868 patients reinforced this warning and showed high-confidence evidence for a risk of bradycardia. In addition, **Beloeil et al. (20)** reported bradycardia occurrence requiring atropine administration as an adverse effect of OFA, as it was more frequent in the dexmedetomidine group than in the remifentanil group.

This is because the association of dexmedetomidine with propofol was shown to increase the risk of hypotension and bradycardia when compared with propofol alone **(21)**.

In contrast to **Shoshiashvili et al. (22)** found that there was a tendency to tachycardia after skin incision and during the first 30 minutes of surgery in non-opioid group.

In this study, regarding the changes in the mean arterial blood pressure, there were no statistically significant differences between both groups at these periods (baseline, pre-induction, at 1, 5, 30, and 60 minutes after induction). There were no difference in baseline MAP in both group ,but in pre induction period MAP increased slightly due to anxiety and sympathetic nervous system activation , then after induction of anesthesia MAP decreased in both group simultaneously due to the vasodilator effect of anesthetic drugs.However, the MBP was significantly lower in the OFA group than in the OBA group at 90 and 120 minutes after induction, at end of surgery, at extubation, as well as one, two, and four hours after surgery, most likely due to the vasodilator effect of lidocaine infusion in OFA group as well as dexmedetomidine infusion as it blocks the sympathetic reaction to surgical injury and pain , so maintaining blood pressure stable.

Similarly, **Soudi et al. (23)** stated that the intraoperative hemodynamic events showed no significant difference between the 2 groups except for hypotension in the OFA group which was not associated with bradycardia. **Ibrahim et al. (24)** found that concerning the hemodynamic changes (MAP), there was no statistically significant difference in the MAP between the two studied groups postoperatively in the PACU. In addition, **Choi et al. (25)** compared the effect of opioid-free analgesia with 80 patients, opioid based anesthesia techniques using dexmedetomidine or fentanyl and propofol TIVA and its effect on stability of hemodynamic on elective laparoscopic cholecystectomy. They found that there was no statistically significant difference in the MAP between the two studied groups postoperatively in the PACU.

In disagreement with **Shoshiashvili et al. (22)** who found that there was a tendency to increase in the MAP after skin incision and during the first 30 minutes of surgery in non-opioid group. They stated that in most of different types of abdominal surgery, head and neck surgery and breast surgery cases, OFA is possible, but opioids supplements give a better hemodynamic stability.

In addition, the results of the current study are in disagreement with **Guinot et al. (26)** performed a retrospective matched cohort study (1:1) on cardiac surgery patients with cardiopulmonary bypass between 2018 and 2019. Patients were divided into two groups: OFA (lidocaine, dexamethasone and ketamine) or opioid anaesthesia (sufentanil). They reported that OFA for cardiac surgery was related to higher incidence of increased blood pressure. This could be explained that they applied different surgery and regimens.

Lavand'homme (27) stated that the intra-operative opioids achieve hemodynamic stability. They block the sympathetic reaction to surgical injury while maintaining blood pressure and heart rate. However, very specific drugs administer to blunt the sympathetic reaction to the surgical stress. Among these drugs which modulate the sympathetic nervous system, α2-adrenergic agonists (clonidine, dexmedetomidine) and β-receptor antagonists (e.g. esmolol) that can treat the acute hemodynamic reaction to surgical stress.

A clinically useful marker that reflects opioid-induced pro-inflammatory actions is the elevated C-reactive protein (CRP). It is a protein produced by the liver, and its level increases in response to inflammation **(28)**.

In the current study, there were no significant differences between both groups regarding the CRP serum levels at pre-induction interval and at the end of operation. However, the CRP level was significantly lower in the OFA group than in the OBA group at 2 and 24 hours after surgery periods. Moreover, there were no significant differences between both groups regarding the TLC levels at pre-induction, end of operation and 2 hour after surgery periods while it was significantly lower in the OFA group than in the OBA group at 24 hours after surgery. Furthermore, regarding the neutrophil and lymphocyte count at pre-induction, end of operation and 2 hour after surgery periods while it was significantly lower in the OFA group than in the OBA group at 24 hours after surgery. This is due to the anti-inflammatory effect of the each component of OFA (ketamine, lidocaine, dexmedotimidine) , through inhibiting immune reaction-induced proinflammatory cytokine production, and decrease blood levels of, CRP, tumor necrosis factor, and/or inducible nitric oxide synthase .

Many inflammatory mediators produced by leucocytes and endothelial cells will elicit pain, which can be counteracted by endogenous opioid peptides in the peripheral nerve terminals. Inflammatory reactions arise postoperatively leading to activation of pain receptors. Regional blocks can elicit complete blockade of impulses reaching the hypothalamus **(15,16)**.

Opium and opioids have been used since ancient times to relieve pain, which is one of the major signs of inflammation, and currently they are the most commonly used drug for pain relief **(29)**. It has been shown that opioid-mediated analgesia is mainly elicited via activation of peripheral opioid receptors, and anti-inflammatory actions of opioids, in addition to their analgesic effects, are produced through attenuation of the release of excitatory proinflammatory neuropeptides from peripheral nociceptors **(30,31)**. However, it has also been reported that, in contrast to their anti-inflammatory actions, opioids interact with opioid receptors on the membranes of immune cells and alter cytokine production, ultimately inducing a pro-inflammatory state **(32)**.

Ghazavi et al. (33) and **Nabati et al. (34)** studies have reported that CRP levels may be elevated in opioid induced pro-inflammatory states. Moreover, **Chopan and Littenberg (35)** had reported that compared to non-opioid users, plasma CRP level was elevated in the opioid users.

Similarly, **Cabellos et al. (36)** suggested a correlation between opioid dosage and CRP level. In addition, associations between CRP levels and surgical stress and postoperative recovery have been reported. Accordingly, CRP levels may be associated with patients' postoperative opioid requirements and pain scores, and correlations may exist between

perioperative CRP levels and an increase in CRP levels, and a patient's opioid analgesic requirements and severity of postoperative pain.[134]

Rogers et al. (32) reported that opioid receptors are members of the G-protein coupled receptor family and the activation of an opioid receptor may decrease the activation of chemokine receptors. This desensitization may increase inflammatory cytokines, including CRP, and this process may be seen as a homeostatic response.

We acknowledge that there are some potential pitfalls in the study; the first limitation was that the small study group size. Secondly; despite the different definitions of opioid-free anesthesia that can be found in the literature or in practice (with or without α2 agonists/ketamine/local anesthetics), previous studies have suggested that α_2 agonists especially dexmedetomidine, could provide the hemodynamic stability traditionally provided by intraoperative opioids. However, definition of opioid-free anesthesia in the present study (multimodal anesthesia as ketamine, lidocaine, and dexmedetomidine) is not definitive, and other ways to administer opioid-free anesthesia have to be explored.

CONCLUSION:

OFA practice is associated with a reduction of systemic inflammatory stress responses, better analgesic profile, a decrease in postoperative opioid-related adverse events, in addition to better hemodynamic stability and an enhanced functional outcome in the patients undergoing elective oncologic abdominal surgeries. However, while the OBA group had a significantly higher incidence of urinary retention, ileus, nausea and vomiting than in the OFA group.

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Author contribution: Authors contributed equally in the study.

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