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Efficacy of dexmedetomidine-based opioid-free anesthesia on the control of surgery-induced inflammatory response and outcomes in patients undergoing open abdominal hysterectomy

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ABSTRACT

Objectives: To compare the effect of opioid-based (OB-GA) versus opioid-free intraoperative analgesia during general anesthesia (OF-GA) and epidural anesthesia (EA) during open abdominal hysterectomy on pro-inflammatory cytokines' levels estimated in blood samples obtained at end of surgery (S2) and 24-hr (S3) postoperative (PO).

Patients: Patients of OF-GA group received loading doses of dexmedetomidine (DEX; 0.6 µg/kg) and Lidocaine (LID; 1.5 mg/kg) and intraoperative (IO) DEX (1 µg/kg) and LID (20 mg/ ml) infusions. GA was provided as sevoflurane inhalational anesthesia and EA was provided as loading dose (15 ml) of 0.5% bupivacaine and intermittent doses if required. The study outcome is the effect of anesthetic techniques on S2 and S3-samples' serum cytokines' levels.

Results: PO serum cytokines' levels were significantly higher than preoperative levels with significantly higher levels in S2-sample of patients OB-GA patients compared to patients of other groups. In the S3 sample, serum cytokines' levels were decreased after OB-GA but increased after OF-GA and EA. OF-GA provided better IO hemodynamic control and PO lower cytokines' levels, pain scores and consumption of rescue analgesia. Satisfaction scores were significantly higher by OF-GA and LA.

Conclusion: DEX-based OF-GA provided better IO and PO control on surgical inflammatory response with improved PO outcomes regarding analgesia and adverse effects. EA also allowed IO control on cytokines' levels but PO rebound was detected.

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Opioid-free; epidural anesthesia; general anesthesia; hysterectomy; inflammatory cytokines

1. Introduction

Surgery-induced inflammatory reaction with concomitant release of pro-inflammatory cytokines as interleukin (IL)-1β and −6 and tumor necrosis factor-alpha (TNF-α) may seriously affect surgical outcomes and is associated with prolonged hypercatabolic state, irrespective of surgical indication and pathological lesion dealt [1].

General anesthesia (GA) can influence both the immediate and long-term outcomes and the lack of evidence regarding the superiority of total intravenous anesthesia (TIVA) over inhalation anesthesia with regards to immune response to surgery added to the dilemma especially for high-risk patients [2]. The protocols of enhanced recovery after surgery (ERAS) were implemented to attenuate the stress of surgery and facilitate early recovery [3]. The ERAS protocol for patients who received GA entails avoidance of routine use preoperative midazolam, deep anesthesia, use of opioid-sparing approach, and minimization of neuromuscular blocking agents, and appropriate reversal of residual paralysis [4].

The opioid-free anesthesia (OFA) is an opioid-sparing technique, which focuses on multimodal or balanced analgesia, relying on non-opioid adjuncts and regional anesthesia [5]. OFA was applied as an integral part of ERAS protocols to minimize perioperative opioid consumption and promote positive outcomes after surgery [6]. Dexmedetomidine (DEX), a selective alpha$_2$ agonist with analgesic effects acting independently on opioid receptors [7]. DEX is used in conjunction with other non-opioid analgesics for OFA to provide hemodynamic stability during and after surgery [8], creating a satisfactory PO outcome with reduced opioid consumption in the post-anesthesia care unit (PACU) [9].

2. Objectives

Evaluation of the effect of opioid-free general anesthesia (OF-GA), epidural anesthesia (EA) and opioid-based general anesthesia (OB-GA) on the surgical-stress immune response in women assigned for open abdominal hysterectomy.

3. Patients & Methods

The current study prospective comparative study was conducted at Department of Anesthesia, Faculty of

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Medicine, Tanta University from Jan 2019 after approval of the study protocol by the Local Ethical Committee.

All women who had indication for abdominal hysterectomy were clinically evaluated concerning indication for surgery by the gynecologist in charge and then by the anesthetist for the evaluation of their ASA grade, cardiopulmonary status, and spinal examination for the ability to provide epidural anesthesia. Routine laboratory investigations including liver and renal function tests and coagulation profiles were performed in a hospital lab.

4. Exclusion criteria

Patients of ASA grade >II who had cardiac, renal, or hepatic diseases or coagulopathies, contraindications for any of the study drugs, vertebral anomalies, endocrinopathy, body mass index (BMI)>35 kg/m^2 were excluded from the study. Women who required pelvic exenteration or mass salpingo-oophorectomy and hysterectomy were also excluded from the study.

5. Inclusion criteria

Women of ASA grade I–II undergoing abdominal hysterectomy, free of exclusion criteria and signed the written consent to undergo the surgery under any form of anesthesia were enrolled in the study.

6. Sample size calculation

A previous study comparing colorectal surgery using the laparoscopic technique (n = 19) under GA, versus open technique under either OB-GA (n = 18) or OB-GA and EA (n = 20) and reported a significant difference in serum levels of IL-4 between GA alone and combination of GA and EA during open surgery, while for other biomarkers the difference was non-significant [10]. Considering the null hypothesis was as the absence of difference between all groups with a delta of 0.07, moderate effect size of 0.25 among 3 groups, using estimated sample sizes for one way ANOVA F test, the required minimal sample size was 30 subjects per group for a total sample size of 90 subjects to achieve a study power of 80% with α error of 5%. Sample size was calculated by the STATA software (Stata Corp, 2021, Version 17).

7. Randomization

Randomization sequence was created using Excel 2007 (Microsoft, Redmond, WA, USA) with a 1:1 allocation using random block sizes of 2 and 4 by an independent assistant. In this way, sequence generation and type of randomization can be expressed at the same time. For blindness purposes, the generated sequences were transformed as cards carrying group labels (OB-GA, OF-GA, or EA according to the analgesia provided during surgery) put in sealed envelopes and was gave to patient to provide it to the anesthetist. For complete blindness, the clinical pathologist will be blinded about the type of anesthesia received by a patient who donated the blood samples.

8. Preparation of OFA drugs

Drugs were prepared as previously described [11] as follows: dexmedetomidine (DEX) loading dose (0.6 μg/kg) was diluted to a total volume of 10-cc in a syringe labeled DEX and Lidocaine (LID) loading dose (1.5 mg/kg) was diluted to a total volume of 10-cc in a syringe labeled LID. Intraoperative continuous infusions were prepared as DEX infusion containing 1 μg/kg and LID infusion containing 20 mg/ml and were given at rate of 0.2–0.7 μg/kg/h and 1–2 mg/kg/−1 h − 1.

9. Anesthetic protocols

At the pre-anesthetic room, baseline heart rate (HR) and mean arterial blood pressure (MAP) measures were determined. Patients received IV midazolam (0.03 mg/kg) and IV fluid, and were maintained well-oxygenated using oxygen 100% as 5 L /min flow rate.

9.1. General anesthesia

Anesthesia was induced by propofol 2 mg/kg, rocuronium 0.5 mg/kg for patients of OB-GA, while was induced using the loading doses of DEX and LID directly intravenously for patients of OF-GA. For patients of both groups, tracheal intubation was aided by gentle tracheal pressure, and an endotracheal tube measuring 6.5 mm was inserted. After intubation of the trachea, the lungs were ventilated with 100% O_2 in the air using a semi-closed circle system. For patients of the OF-GA group, DEX and LID infusions were applied at a rate of 0.3 ml/kg/h and 2 mg/kg/h, respectively. During surgery, ventilation was controlled with a tidal volume of 6–8 ml/kg, and the ventilatory rate was adjusted to maintain an end-tidal carbon dioxide (pa_{CO2}) of 32–35 mmHg. For intraoperative analgesia fentanyl, 1 μg/kg was given for patients of OB-GA and adjustment of infusions' rates for patients of OF-GA. Anesthesia was maintained with sevoflurane 1.7 MAC and top-up doses of rocuronium if needed. Muscle relaxant was reversed using neostigmine 0.05 mg/kg with atropine 0.01 mg/kg.

9.2. Epidural anesthesia

All patients received preload with 500 ml of lactated Ringer's solution and were positioned in either lateral decubitus or sitting positions according to the

preference of the anesthetist in charge. The epidural space at the level of L_{3-4} or L_{4-5} interspace was identified using the loss of resistance technique. Then, a 20 gauge epidural closed-end multi-orifice catheter (Perifix 401, B. Braun, Melsungen AG) was inserted through an 18-gauge Tuohy needle that was placed at chosen interspace and advanced 3 to 5 cm into the epidural space. A test dose was done by injecting 3 ml of 1.5% lidocaine with epinephrine (1:200000) to rule out the intravascular position of the catheter, which was defined as an increased HR by 20–30 beat/min or systolic blood pressure by 15–20 mmHg. After completion of the epidural procedure, an initial loading dose of 15 ml of 0.5% bupivacaine was injected into the catheter followed by intermittent manual boluses (20–30% of the initial amount) at timed intervals to maintain the desired anesthesia.

10. Intraoperative (IO) and postoperative (PO) monitoring

- Perioperative respiratory rate, Sp_{O2}, HR, and MAP were non-invasively monitored. Hypotension was defined as a reduction of the systolic blood pressure by >20% of preoperative pressure and was treated with the rapid infusion of lactated Ringer's solution and intravenous boluses of ephedrine.
- Patients were transferred to the PACU where oxygen saturation was monitored using pulse oximetry and oxygen (6 L/min) was administered via a face mask in the PACU if indicated. PACU discharge was dependent on Aldrete recovery score [12] that ranges from 0 (comatose patients) to 10 (completely recovered), patients were discharged at a score of ≥8, time till PACU discharge was recorded.
- PO pain severity was assessed using an 11-point numeric rating scale (NRS) with numbers from 0 to 10 where 0 indicates no pain and 10 indicates worst pain imaginable [13]. PO pain was assessed at the time of PACU discharge and 4-hourly for 24-hr. Duration of PO analgesia was defined as the time till 1st request of PO analgesia that was supplied as paracetamol infusion (Injectmole 10 mg/ml infusion; AMRIYA PHARM. IND., Alexandria – Egypt) given at the rate of 10 mg/h, but patients who had NRS pain scores of >4 despite PO analgesia received morphine 5 mg intramuscular.
- PO sedation was assessed using the RAMSAY sedation scale [14] immediately after transfer to PACU, 30-min, and 60-min thereafter and PO nausea and vomiting (PONV) were rated using 4-point nausea and 3-point vomiting scores [15]. Ondansetron 40 mg intravenous injection was given for patients who had severe nausea or vomiting.
- Surgeons' and patients' satisfaction by type of anesthesia and PO analgesia was recorded using a visual analog scale of 0–100 with the higher score the higher is the satisfaction [16].

11. Laboratory investigations

Peripheral venous blood samples; immediately before induction of anesthesia, at end of surgery and 24-hr PO (S1–3 samples), were obtained by venipuncture under complete aseptic conditions, collected in plain tubes, allowed to clot in a warm water bath at a temp of 37°C for 5 minutes, and then centrifuged at 5000 rpm for 2 minutes to separate serum. Serum was collected in Eppendorf tubes and stored at −20°C till estimation of serum interleukin (IL)-1β [17], IL-6 [18], and tumor necrosis factor-α (TNF-α) [19] by quantitative sandwich enzyme immunoassay technique using enzyme-linked immunosorbent assay (ELISA) kits (Abcam Inc., San Francisco, USA; catalog no. ab46052, ab187013 and ab46087, respectively) according to the manufacturer's instructions by quantitative sandwich enzyme immunoassay technique and were read using a 96 well microplate ELISA reader (Dynatech. MR 7000):

12. Study outcome

(1) The primary outcome is the effect of the anesthetic procedure on serum cytokines' levels in S2 and S3 samples.
(2) The secondary outcomes include
   - PO pain score, duration of analgesia, sedation and incidence and severity of PONV
   - Surgeons' and patients' satisfaction by the applied anesthetic procedure.

13. Statistical analysis

Obtained data were presented as mean, standard deviation, numbers, and percentages. Results were analyzed using One-way ANOVA for analysis of variance between groups, paired t-test for analysis within each group, Chi-square test (X^2 test) for analysis of non-numeric data, and Mann–Whitney test for median values. Statistical analysis was conducted using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA) for Windows statistical package. P-value <0.05 was considered statistically significant.

14. Results

The study included 109 patients eligible for evaluation, 19 patients were excluded; four were of ASA grade III, seven patients had BMI>35 kg/m2, three patients were maintained on immunosuppressive drugs, two patients required pelvic exenteration and two patients had autoimmune diseases. Ninety patients were randomly allocated into the three groups and completed the study protocol without IO or PO exclusions

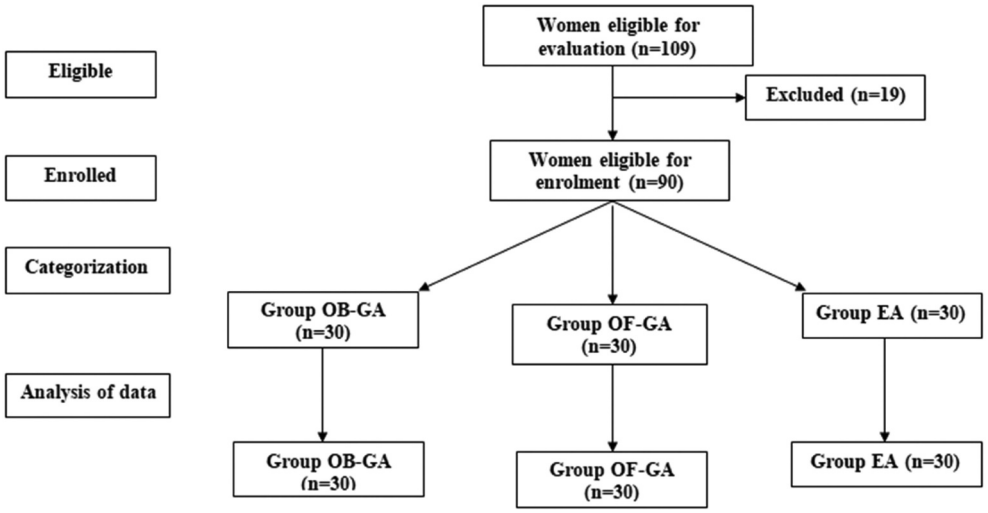

Figure 1. The study flowchart.

(Figure 1). Enrolment and operative data of studied patients showed nonsignificant ($P > 0.05$) differences between the three groups. However, time till PACU discharge was significantly shorter with EA than other modalities, but was significantly longer with opioid-free than with opioid-based anesthesia (Table 1).

Preoperative HR and MAP measures showed non-significant differences between patients of the three group, while IO measures were significantly lower with EA compared to opioid-based or opioid-free anesthesia and with opioid-free than opioid-based anesthesia as shown in Table 2

Serum cytokines' levels in preoperative samples (S1 sample) showed nonsignificant differences between studied patients. In S2 samples of EA patients, estimated serum TNF-α and IL-6 were significantly higher compared to levels estimated in S1 and S3 with significantly higher levels in S3 than in S1 samples. On contrary, serum IL-1β showed nonsignificant differences between the three samples of EA patients. In S2 samples of patients of opioid-based or – free groups, serum levels of the three cytokines were significantly higher than corresponding levels in S1 samples. However, in S3 samples of patients received general anesthesia, the estimated levels of TNF-α and IL-6 were significantly higher, while that of IL-1β were non-significantly higher than their S1 levels, but were lower than their S2 samples. As regards the effect of the anesthetic procedure, serum TNF-α and IL-6 in S2 samples were significantly higher in patients received opioid-based anesthesia compared to patients of other groups with significantly higher levels in samples of patients received opioid-free anesthesia. Serum levels of TNF-α were significantly higher in S3 samples of patients of opioid-based group compared to patients of other groups that showed nonsignificant difference in favor of opioid-free anesthesia. Serum levels of IL-6 were significantly lower in S3 samples of patients of opioid-based group compared to patients of other groups that showed nonsignificant difference in favor of epidural anesthesia. On the other hand, serum levels of IL-1β showed nonsignificant differences between samples of patients of the three groups, apart from the significant difference between S2 samples of patients who received opioid-based or -free anesthesia (Table 3).

Throughout 24-h PO, mean values of time-series NRS pain scores were significantly lower with opioid-free than with opioid-based and epidural anesthesia and with epidural than opioid-based anesthesia and the average of the 24-h NRS pain score was significantly lower after opioid-free than after opioid-based and epidural anesthesia with non-significantly lower score after epidural anesthesia. Mean duration till the 1st request of rescue analgesia was significantly longer

Table 1. Demographic, clinical, and operative data of patients of the three groups.

Variables	Group	Opioid-based general anesthesia (n = 30)	Opioid-free general anesthesia (n = 30)	Epidural anesthesia EA (n = 30)
Age (years)		50 ± 4	50 ± 5	49 ± 5
Body mass index (kg/m^2)		31 ± 1	30 ± 2	30 ± 2
ASA grade; I:II		23:67	19:11	20:10
Indication	Uterine myoma	19 (63%)	20 (67%)	18 (60%)
	Endometrial hyperplasia	8 (27%)	6 (20%)	10 (33%)
	Endometrial carcinoma	3 (10%)	4 (13%)	2 (7%)
Operative time (min)		125 ± 13	129 ± 14	126 ± 12
PACU stay (min)		10 ± 2	12 ± 2	9 ± 1

Data are presented as mean, standard deviation, ratios, numbers & percentages

Table 2. Intraoperative hemodynamic data of patients of the three groups.

variables	Group	Opioid-based general anesthesia (n = 30)	Opioid-free general anesthesia (n = 30)	Epidural anesthesia EA (n = 30)
HR	T0	75 ± 7	75.9 ± 7	76 ± 5
	Induction	83 ± 6	79.3 ± 7*	78 ± 4
	Intubation	90 ± 5*	85.8 ± 6†	75 ± 4†
	15-min	83 ± 4*	79 ± 5†	70 ± 3.4†
	30-min	78 ± 4*	75.2 ± 5†	64 ± 4†
	60-min	72 ± 3†	66.7 ± 6†	60 ± 4†
	90-min	68 ± 4†	59 ± 6†	58 ± 4.1
	Extubation	76 ± 4†	67 ± 5.9†	57 ± 3.9†
	PACU	70 ± 3	73 ± 5.2†	60 ± 3.7†
MAP	T0	80 ± 5	82 ± 5.3	80 ± 9
	Induction	83 ± 5	84 ± 4.9†	76 ± 8†
	Intubation	88 ± 5	87 ± 5†	70 ± 9
	15-min	72 ± 4	70 ± 4*	67 ± 8
	30-min	68 ± 4†	60 ± 4*	63 ± 8
	60-min	64 ± 5†	56 ± 4*	60 ± 9*
	90-min	67 ± 4†	52 ± 3†	58 ± 9*
	Extubation	77 ± 4†	66 ± 5†	55 ± 9†
	PACU	74 ± 4	73 ± 4†	55 ± 7†

Data are presented as mean, standard deviation; HR: Heart rate; MAP: Mean arterial pressure; T0: preoperative; PACU: Post-anesthetic care unit; *: indicates significance at $p < 0.05$; † indicates significance at $p < 0.001$

Table 3. Serum cytokines' levels estimated in the three samples obtained from patients of the three groups.

variables	Group	Opioid-based general anesthesia (n = 30)	Opioid-free general anesthesia (n = 30)	Epidural anesthesia EA (n = 30)
TNF-α (ng/ml)	S1	3.9 ± 0.3	4.1 ± 0.7	4.1 ± 0.5
	S2	7.3 ± 0.9†	5.6 ± 0.89†	4.9 ± 0.8*
	S3	6.1 ± 0.9†	5 ± 0.7*	5.3 ± 0.8
IL-6 (ng/ml)	S1	10 ± 2.6	9.5 ± 3.6	9.7 ± 3.5
	S2	15.7 ± 2.2†	13.9 ± 3.6*	11.9 ± 3*
	S3	13.5 ± 2.1*	17.7 ± 4.5*	16.3 ± 3.4
IL-1β (ng/ml)	S1	4.6 ± 1.9	4.4 ± 1.4	4.5 ± 1.8
	S2	6.2 ± 1.6	5.578 ± 1.28*	5.157 ± 1.6
	S3	5.6 ± 1.6	5.2 ± 1.3	5.4 ± 1.6

Data are presented as mean, standard deviation; S1: Preoperative sample; S2: Sample obtained at end of surgery; S3: Sample obtained 24-hr after surgery; TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; IL-1β: Interleukin-1β; *: indicates significance at $p < 0.05$; † indicates significance at $p < 0.001$

after opioid-free than after the opioid-based and epidural anesthesia and was significantly longer after epidural than opioid-based anesthesia. Moreover, the frequency of requests of morphine rescue analgesia was significantly higher after opioid-based anesthesia than after other procedures and after epidural than after opioid-free anesthesia (Table 4).

All patients who received epidural anesthesia were transferred awake to PACU. Patients who received opioid-free anesthesia showed significantly higher sedation scores till 60-min after PACU transfer than patients of other groups, while patients who received opioid-based anesthesia had significantly higher sedation score at time of PACU transfer, and thereafter the

Table 4. PO data of patients of the three groups.

variables	Group		Opioid-based general anesthesia (n = 30)	Opioid-free general anesthesia (n = 30)	Epidural anesthesia EA (n = 30)
PO pain data	Average of 24-h NRS pain score		1.6 ± 0.3	0.6 ± 0.4†	1.6 ± 0.3
	Duration of PO analgesia (min)		123 ± 33†	358 ± 73†	241 ± 62†
	Number of doses of morphine	0	0	6 (20%)	0
		1	3 (10%)	16 (53.3%)	23 (76.6%)
		2	24 (80%)	8 (26.7%)	5 (16.7%)
		3	3 (10%)	0	2 (6.7%)
At PACU sedation scores	At time of transfer		2.6 ± 0.6†	3.8 ± 0.7†	1.6 ± 0.5†
	30-min after transfer		1.7 ± 0.5	3.2 ± 0.5†	1.6 ± 0.5
	60-min after transfer		1.8 ± 1*	2.3 ± 0.5	1.6 ± 0.5†
PO nausea & vomiting scores	Nausea scores	0	0	19 (63.3%)	14 (46.7%)
		1	15 (50%)	9 (30%)	12 (40%)
		2	10 (33.3%)	2 (6.7%)	4 (13.3%)
		3	5 (16.7%)	0	0
	Vomiting scores	0	22 (73.3%)	28 (93.3%)	27 (90%)
		1	6 (20%)	2 (6.7%)	3 (10%)
		2	2 (6.7%)	0	0
Satisfaction scores	Surgeons		83 ± 7.4†	93.1 ± 3.3	90.4 ± 3.2
	Patients		77.1 ± 8.3	89.8 ± 4.4†	81.6 ± 7.8*

Data are presented as mean, standard deviation; numbers & percentages; PO: Postoperative; NRS: Numerical rating scale; *: indicates significance at $p < 0.05$; † indicates significance at $p < 0.001$

difference was non-significant in comparison to patients of epidural group. Fifty-seven patients (63.3%) had nausea and 13 patients (14.4%) had vomiting with a significantly higher frequency and higher scores among patients who received opioid-based anesthesia compared to patients of other groups, which showed nonsignificant difference (Table 4).

The mean values of surgeons' and patients' satisfaction scores were significantly higher for opioid-free and epidural anesthesia than for opioid-based anesthesia with non-significantly higher surgeons' but significantly higher patients' scores for opioid-free than epidural anesthesia (Table 4).

15. Discussion

Serum cytokines' levels in the sample obtained at the end of surgery were significantly higher than preoperative levels of all patients. This finding illustrates the impact of surgery on the inflammatory immune milieu and indicated that surgery per se is an inflammatory condition and supports the results of experimental studies that documented the association of surgery with a systemic proinflammatory response [20–24]. Also, the detected higher cytokines levels immediately after surgery in S2 sample coincided with previous clinical trials, which documented that laparotomy initiates a surgical-induced pro-inflammatory reaction involving immune activation, cortical excitability, hypercatabolic status and coagulopathy [25,26].

The surgically-induced inflammatory response was amplified by the use of general anesthesia and opioid analgesia as evidenced by the significantly lower cytokines' levels in S2 samples of patients who received opioid-free compared to patients who received opioid-based anesthesia and the decreased cytokines' levels in S3 samples of patients who received OBA indicated the deleterious effect of opioids on immune milieu. On the other hand, the increased cytokines' levels in S3 samples of patients who received opioid-free anesthesia indicated an ameliorating effect of the used drugs, which when the effect disappeared the inflammation flourished.

In support of these assumptions, multiple studies found the use of adjuvant blocks reduced opioid concentration and PO inflammatory response by limiting concentrations of pro-inflammatory cytokines [27,28]. Another study reported nonsignificant differences in serum cytokines' levels with the use of opioid-based volatile general or total intravenous anesthesia using propofol/remifentanil [29] and another study found the use of opioid-free anesthesia reduced perioperative serum levels of IL-12 and TNF-α for 48-hr than opioid-based anesthesia and concluded that opioids trigger changes in inflammatory cytokine release [30].

In a trial to explore the mechanisms of the inflammatory effect of opioids, an in-vitro study found the application of exogenous opioids stimulates the release of opioid peptides by neutrophils, macrophages, and T-cells with subsequent activation of the release of cytokines [31]. Another experimental study found opioid receptor agonists activate the Toll-like receptor 4 signaling pathway leading to nuclear factor κ-B cells expression and the production of the pro-inflammatory cytokines [32].

Epidural anesthesia (EA) showed superior control on surgery-induced inflammatory response in comparison to other anesthetic procedures with special regard to TNF-α and IL-6, such effect assured the deleterious effect of GA with or without opioids on the inflammatory response to surgery. In support of the ameliorative role of EA, serum cytokines' levels were significantly increased at 24-hr after surgery than in preoperative and immediately PO samples. Similarly, previous two studies found the combination of EA and TIVA [33] or GA [34] significantly attenuated the intraoperative stress response and serum cytokines' levels. Also, a previous comparative study between remifentanil and EA during one-lung ventilation anesthesia detected higher cytokines' concentrations with remifentanil than with [35].

The duration of PO analgesia was significantly longer and analgesic requirements were significantly lower with opioid-free than with epidural and opioid-based anesthesia with a significant difference in favor of EA. The better PO analgesia with opioid-free anesthesia could be attributed to the effect of DEX and LID infusions with special importance for DEX which provided a longer duration of sedation allowing a calm PO period and longer duration of analgesia. Moreover, the ameliorated IO inflammatory response with OFA could be attributed to the use of DEX. In line with this assumption, previous recent studies found perioperative DEX administration can enhance pain management, promote surgical recovery, and is associated with a reduction in anxiety, perioperative stress, inflammation, PONV, shivering, and cognitive dysfunction [36,37].

16. Conclusion

Dexmedetomidine-based intraoperative analgesia provided superior perioperative control on surgery-induced inflammatory response, prolonged PO analgesia with reduction of PO morphine consumption than opioid-based intraoperative analgesia. Epidural anesthesia provided significant intraoperative control on serum cytokines' levels than OB-GA, but reactionary PO increase was a disadvantage for EA.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

Limitation

The study is a single-center study and this affected the sample size.

Recommendation

More comparative multicenter studies were required to establish the obtained results. Also, combined EA and PO dexmedetomidine infusion must be tried to prolong the ameliorative effect of EA and to take the advantages of DEX especially for immuno-compromised patients.

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