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Opioid-Free Anesthesia for Laparoscopic Hysterectomy: Is it Appropriate?

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Abstract

Objective: To evaluate intraoperative (IO) and postoperative (PO) outcome of women assigned to laparoscopic hysterectomy under opioid-free anesthesia (OFA) in comparison to opioid-based anesthesia (OBA).

Patient and Methods: 72 women were randomly divided into OBA and OFA groups according to the provided IO analgesic regimen. OBA patients received Fentanyl (FEN) as loading and Remifentanyl (REM) infusion as maintenance analgesia. OFA patients received preoperative parecoxib sodium for preparation, dexmedetomidine (DEX) and lidocaine (LID) as loading and maintenance analgesia. Study Outcomes included the frequency of patients developed IO deviated mean arterial pressure (MAP) measures by >20% of baseline measures, duration of surgery and time till fulfilling criteria for PACU discharge, duration of PO analgesia, time till 1st ambulation, PO complications and hospital stay.

Results: Demographic data and surgical characteristics were comparable in all groups. The D group showed delay in onset for first call for analgesia (900±60.9min) while M and K groups results were (600±33.4min) and (350±17.4min) respectively, all of the group's results were statistically significant than the control group result (260±14.3min).

Results: MAP measures during and 30-min after abdominal insufflations were significantly higher in patients of OFA than patients of OBA. Among 216 MAP readings, increased MAP measures by >20% of baseline measure was recorded in 10 (4.6%) versus 3 (1.4%) readings in OFA and OBA groups, respectively with a non-significant difference (p=0.091) between both groups. Duration till 1st ambulation was significantly shorter with OFA compared to OBA, while duration till 1st request of rescue analgesia was significantly longer with OFA, while the frequency of patients requested more rescue analgesia was significantly higher with OBA than OFA. PONV was reported in 53 patients and 17 patients required anti-emetic therapy with significantly higher incidence with OBA compared to OFA group.

Conclusion: The applied protocol for OFA provided satisfactory IO analgesia and control of surgery-induced pressor reflexes. Also, it allowed reduction of PO analgesic consumption with early ambulation and reduced PONV that were reflected as shorter PO hospital stay.

Keywords: Opioid-free anesthesia; Parecoxib; Dexmedetomidine; Lidocaine; Remifentanyl; Laparoscopic hysterectomy

Introduction

Hysterectomy is the most common major gynecological procedure in women [1], but hysterectomy for enlarged uteri is considered a challenge for gynecologic surgeons, due to the limit of exposure to surgical spaces [2]. Minimally invasive approaches as total laparoscopic hysterectomy should be used wherever possible [1] as it is the standard of care in majority of women diagnosed with endometrial cancer [3] and is feasible for enlarged uteri [2]. Postoperative (PO) pain remains one of the most common challenges following inpatient and outpatient surgeries [4]. Opioids are the most potent drugs used to control severe pain [5], however, surgical care episodes place opioid-naive patients at risk for transitioning to new persistent PO opioid use [6].

Opioids are frequently associated with adverse events such as dizziness, drowsiness [7], high incidence of PO nausea and vomiting, which varies from 20%-60% [8] or constipation which disturbs PO recovery and extends the duration of hospital stay [7].

With increased awareness of both short- and long-term problems associated with liberal perioperative opioid administration, the need for routinely and clinically feasible alternatives is greater than ever [9]. Implementation of multimodal analgesic regimen achieved equivalent and effective pain control aiming to reduce the reliance on opioid-based medications [10]. The application of enhanced recovery pathways promoted opioid-free and multimodal analgesia [11] and allowed

decreased perioperative opioid use [6]. Opioid-free anesthesia (OFA) has gained in popularity to enhance early recovery and to spare opioid use for the PO period [12]. OFA was found to be safe, provided comfort during the immediate PO period equal to after conventional anesthesia and may provide reduced pain during the first 24 PO hours [13].

Dexmedetomidine (DEX) is α2-adrenergic sedative-hypnotic medication [14] with analgesic, sedative and sympatholytic properties and a lack of respiratory depression [15], so it is used as an adjunct to general anesthesia [14]. Also, DEX can effectively reduce the incidence of PO cognitive impairment with high safety for circulatory function [16].

Hypothesis

Opioid-free anesthesia improves postoperative outcome of women underwent laparoscopic hysterectomy and hastens recovery and home-discharge without compromising operative outcome.

Objective

Evaluation of intraoperative (IO) and PO outcome of women assigned to laparoscopic hysterectomy under OFA compared to opioid-based anesthesia (OBA).

Setting

Departments of Anesthesia and Gynecology, Benha & Tanta Universities, Ministry of Health, Tanta, Egypt.

Design

Prospective clinical trial.

Patients and Methods

The study protocol was approved by the Local Ethical Committees and patient and her husband signed written fully informed consents according to the declaration of Helsinki. All women assigned for hysterectomy were eligible for evaluation, patients with ASA grade >II, body mass index (BMI) >35kg/m^2, cardiac or chest diseases, previous open abdominal surgery, history of treatment or surgery for hiatus hernia, hypersensitivity to the drugs to be used, requiring total hysterectomy or pelvic excentration or refusing laparoscopic surgery were excluded from the study. All eligible women were clinically evaluated for demographic and baseline clinical data collection, underwent laboratory and radiological workup for assurance of inclusion and exclusion criteria.

Randomization and grouping

Patients were randomly allocated into two groups; control group included women assigned to receive opioid-based anesthesia (OBA group), while study group included women assigned to receive opioids-free anesthesia (OFA group). For randomization, cards carrying group label were prepared by an assistant blinded about the significance of the label and cards were put in envelops free of marks and closed. On arrival to pre-anesthetic room, patient was asked to choose a card that was opened by anesthetist in charge.

Preparation of Study drugs

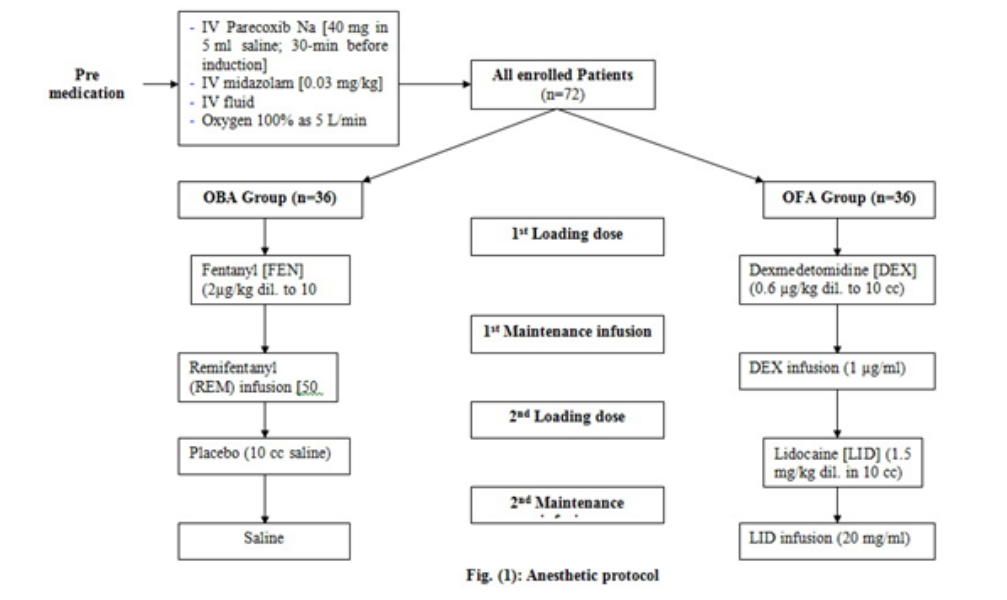

Figure 1: Anesthetic protocol.

Study drugs were freshly prepared by hospital clinical pharmacist blinded about the significance of labels. Drugs were prepared according to the protocol that previously documented by Bakan et al. [17]. For each group, two 10-cc syringes were prepared to provide the loading dose (L-1 & L-2) and two infusion fluid bottles for maintenance of anesthesia (M-1 & M-2)

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a) Opioid-based anesthesia (OBA) group: Fentanyl (FEN) loading dose was prepared as 2μg/kg, diluted to a total volume of 10cc in a syringe labeled as CL-1 and CL-2 syringe was filled by 10-cc saline as placebo. Remifentanyl (REM) infusion was prepared as 50μg/ml, was labeled as CM-1 and a bottle of saline free of additives was prepared as CM-2 infusion.

b) Opioid-free anesthesia (OFA) group: Dexmedetomidine (DEX) loading dose was prepared as 0.6μg/kg, diluted to a total volume of 10cc in a syringe labeled as SL-1 and Lidocaine (LID) loading dose was prepared as 1.5mg/kg in a syringe labeled SL-2. DEX infusion was prepared as 1μg/ml, was labeled as SM-1 and LID infusion was prepared as 20mg/ml, was labeled as SM-2 (Figure 1).

Anesthetic protocol

a) At pre-anesthetic room, baseline heart rate (HR) and mean arterial blood pressure (MAP) were determined non-invasively. Parecoxib sodium 40 mg diluted with 5ml of saline was injected intravenously (IV) 30-min before induction of anesthesia. Patients were premedicated with IV midazolam (0.03mg/kg), received IV fluid and were maintained well-oxygenated using oxygen 100% as 5L/min flow rate.

b) On arrival to the theater, patients of both groups received the prepared drugs according the chart shown in Figure 1 as follows:

c) 1st loading doses (CL-1 and SL-1 syringes containing Fen & DEX loading dose, respectively) were injected in 10-min.

d) CM-1 and SM-1 infusions of REM & DEX, respectively, were started at rate of 0.3 ml/kg/h.

e) 2nd loading doses (CL-2 and SL-2 syringes containing plain saline & LID, respectively) were infused simultaneously with induction dose of propofol (1.5mg/kg)

f) Immediately, CM-2 and SM-2 infusions of plain saline and LID, respectively were started simultaneously with propofol infusion at rate of 10mgl/kg/h.

g) IV rocuronium (0.6 mg/kg) was injected to facilitate tracheal intubation.

h) After intubation of the trachea, the lungs were ventilated with 100% O2 in air using a semi-closed circle system. During surgery, ventilation was controlled with a tidal volume of 6-8ml/kg, and the ventilatory rate was adjusted to maintain an end-tidal carbon dioxide (paCO2) of 32-35mmHg. Patients were continuously non-invasively monitored for MAP and HR.

i) Infusions M-1 and M-2 were maintained at the initial rate, but propofol infusion was adjusted to 3-12mg/kg/hr to maintain HR and MAP within ±20% of baseline MAP till skin closure.

j) After skin closure, any residual neuromuscular blockade was reversed by neostigmine 0.05mg/kg and atropine 0.02mg/kg and tracheal extubation was performed when patients achieved a regular spontaneous breathing and patients were transferred to the post-anesthesia care unit (PACU).

k) At PACU, oxygen saturation was monitored using pulse oximetry and oxygen (6L/min) was administrated via a facemask in the PACU if indicated. PACU discharge was dependent on Aldrete recovery score that ranges from 0 (comatose patients) to 10 (complete recovery), patients were discharged at score of ≥8 [18].

Postoperative care

Postoperative 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 [19]. PO pain was assessed at time of PACU discharge before the 2nd dose of parecoxib and 4-hourly for 24-hr. Duration of PO analgesia was defined as time till 1st request of rescue analgesia that was supplied as IV parecoxib (20mg diluted in 5cc saline). Frequency of requests of rescue analgesia was also determined.

Study Outcomes

Primary outcome

a) The frequency of patients developed IO deviated MAP measures by >20% of baseline measures and necessitated interference.

Secondary outcome

a) IO mean HR and MAP determined before and after intubation and at time of pneumoperitoneum, and five minutely till uterus extraction

b) Duration of surgery, anesthesia and time till fulfilling criteria for PACU discharge

c) Frequency of requests of rescue analgesia, time till 1st ambulation, PO complications and PO hospital stay.

Results

One hundred and seven patients were eligible for evaluation, 35 women were excluded, 72 women were equally divided into two groups (Figure 2). There was non-significant (p>0.05) difference between both groups as regards enrolment data determined at time of enrolment as shown in Table 1.

Heart rate and MAP measures that were recorded preoperatively, before induction of anesthesia and after intubation showed non-significant difference between patients of both groups. HR measures were increased during abdominal insufflation in patients of both groups but were non-significantly higher in patients of OFA group than those of OBA group. During surgery and at time of extubation HR measures were non-

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significantly higher in patients of OFA group. MAP measures during and 30-min after abdominal insufflation were significantly higher (p=0.041 & 0.0002, respectively) in patients of OFA than patients of OBA, while at 45-min after insufflation and at time of extubation, MAP measures were non-significantly higher in OFA group compared to OBA group (Table 2).

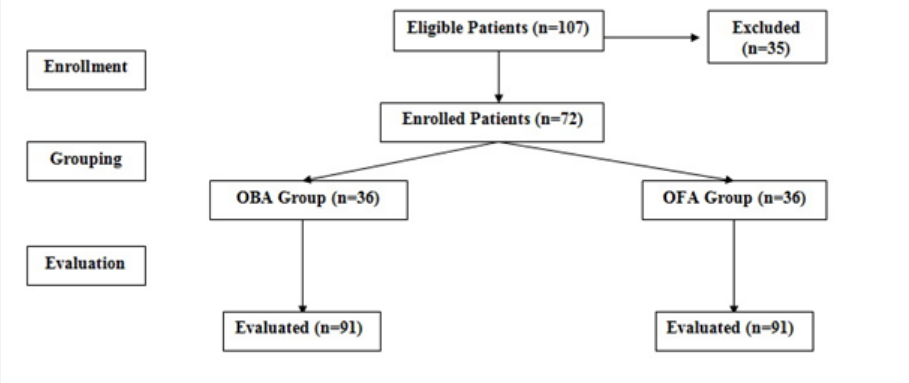

Figure 2: Flow chart of the study.

Table 1: Baseline data of enrolled women.

Data		OBA (n=36)	OFA (n=36)	P value
Age (years)		52.4±8.1	50.4±6.6	0.371
BMI data	Weight (kg)	81.5±7.9	82.5±8.8	0.595
	Height (cm)	169.1±4.2	169.5±3.2	0.661
	BMI (kg/m^2)	28.5±2.9	28.7±3.1	0.463
ASA grade	ASA-I	28 (77.8%)	26 (72.2%)	0.552
	ASA-II	8 (22.2%)	10 (27.8)	
Indication for surgery	Fibroid	21 (58.3%)	23 (63.9%)	0.629
	DUB	15 (41.7%)	13 (36.1%)	
Fasting blood glucose (mg/dl)		82.7±8.4	84.1±6	0.078

Data are presented as mean ± SD, numbers, percentages; BMI: Body mass index; DUB: Dysfunctional uterine bleeding; P indicates the significance of difference between both groups; p>0.05: indicates non-significant difference.

Table 2: Preoperative and intraoperative HR and MAP measures of patients of both groups.

Variable	Time	OBA (n=36)	OFA (n=36)	P Value
Heart Rate (beats/min)	Preoperative	82.8±4	80.7±6.3	0.103
	At time of induction	76.2±4.7	74.5±5.3	0.159
	At time of intubation	84.5±3.9	86.4±4.6	0.061
	Before abdominal insufflation	70±6.2	72.3±6.5	0.128
	At time of abdominal insufflation	73±5.4	75.2±7.1	0.151
	30-min after abdominal insufflation	72±4.6	73.3±6.1	0.311
	45-min after abdominal insufflation	74.4±7.3	76.4±7.5	0.243
	At time of extubation	76.4±7.5	79.5±7	0.077
MAP (mmHg)	Preoperative	88.9±3	89.5±3.1	0.369
	At time of induction	92.3±2.8	93.1±3	0.237
	At time of intubation	92.6±2.9	93.5±2.7	0.207
	Before abdominal insufflations	94.8±2.7	96±5.5	0.225
	At time of abdominal insufflations	95±2.4	96.6±4.4	0.041
	30-min after abdominal insufflations	90.5±6.6	95.2±2.8	0.0002
	45-min after abdominal insufflations	93.2±2.3	92.8±2.9	0.467
	At time of extubation	92.6±2.7	93.5±2.7	0.141

Data are presented as mean±SD; P indicates the significance of difference between both groups; p>0.05: indicates non-significant difference; p<0.05: indicates significant difference.

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Considering the primary outcome, all patients of OFA group showed increased MAP measures recorded throughout operative time in relation to baseline MAP. However, MAP estimated just before abdominal insufflations was increased by >20% of baseline measure in 3 patients (8.3%), in 5 patients (13.9%) at time of abdominal insufflations and in one patient (2.8%) at 30 and 45-min after abdominal insufflations. Thus, increased MAP measures by >20% of baseline measure was recorded in 10 readings of 216 readings for a rate of 4.6%. Among, patients of OBA group, MAP was increased by >20% of baseline measure in three readings only (1.4%), while was decreased than baseline measures in 12 readings (5.6%). Comparison of percentage of MAP change in relation to baseline measures in both groups, the difference was significant (p=0.008) only at 30-min after abdominal insufflations secondary to development of decreased MAP in patients of OBA group. All other calculated percentages of MAP changes showed non-significant difference between patients of both groups (Table 3, Figure 3).

Table 3: Percentage of change of intraoperative MAP measures of patients of both groups in relation to their preoperative measures.

Time	OBA (n=36)	OFA (n=36)	P Value
At time of induction	3.9±1.4	4±1.6	0.619
At time of intubation	4.2±1.6	4.4±1.4	0.575
Before abdominal insufflations	6.8±5.3	7.4±6.9	0.678
At time of abdominal insufflations	6.9±4.3	8.1±6.3	0.352
30-min after abdominal insufflations	2±8.5	6.4±4.7	0.008
45-min after abdominal insufflations	5±4.7	3.7±3.1	0.185
At time of extubation	4.2±1.7	4.5±1.6	0.441

Data are presented as mean±SD; P indicates the significance of difference between both groups; p>0.05: indicates non-significant difference; p<0.05: indicates significant difference.

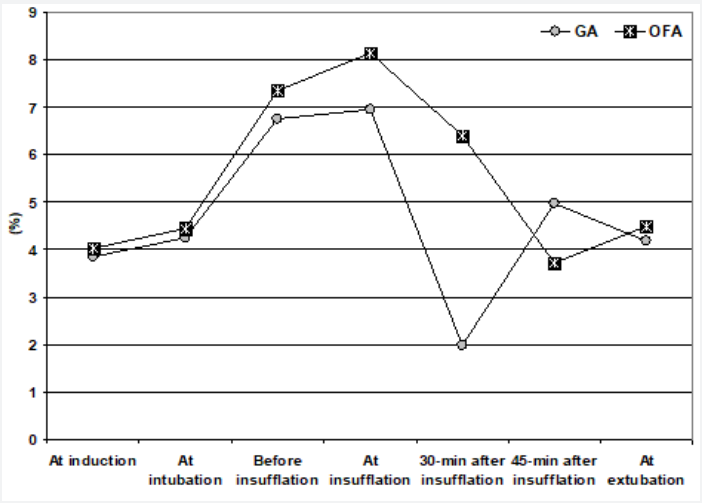

Figure 3: Mean percentage of change of MAP in relation to base line MAP.

Mean operative time and time for being ready to discharge to PACU were non-significantly shorter, while duration till 1st ambulation was significantly shorter with OFA compared to OBA. On contrary, duration till 1st request of rescue analgesia was significantly longer with OFA, while the frequency of patients requested more rescue analgesia was significantly higher with OBA than OFA. Only 18 patients complained of PO shivering; 12 with OBA and 6 with OFA with non-significantly higher frequency with OBA. On the other hand, 53 patients complained of PO nausea or nausea and vomiting; 31 in OBA and 22 in OFA groups, and 17 patients required anti-emetic therapy; 13 in OBA and 4 in OFA groups with significantly higher incidence with OBA compared to OFA group (Table 4).

Table 4: Operative and postoperative data of patients of both groups.

Items	OBA (n=36)	OFA (n=36)	P Value
Operative time (min)	234±44.4	227±50	0.548
Time till PACU discharge (min)	27.9±6.5	25.1±5.5	0.054
Duration till 1st ambulation (min)	95.3±11.7	85.4±14.7	0.002
Duration till 1st request of rescue analgesia (min)	66.6±13.9	76.9±17.8	0.007

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Number of requests of rescue analgesia		One	12 (33.3%)	20 (55.5%)	0.023
		Two	16 (44.4%)	15 (41.7%)	
		Three	8 (22.3%)	1 (2.8%)	
PO complications	Shivering	No	24 (66.7%)	30 (83.3%)	0.174
		Yes	12 (33.3%)	6 (16.7%)	
	PONV	No	5 (13.9%)	14 (38.9%)	0.033
		Yes	31 (86.1%)	22 (61.1%)	
	Antiemetic therapy	No	23 (63.9%)	32 (88.9%)	0.026
		Yes	13 (36.1%)	4 (11.1%)	

Discussion

Opioid-free anesthesia (OFA) ameliorated but could not totally control the pressor response to intubation and abdominal insufflations as manifested by increased MAP measures recorded throughout operative time in relation to baseline MAP. On contrary, opioid-based anesthesia (OBA) allowed better control for these pressor responses as evidenced by the decreased percentage of increased MAP in relation to preoperative MAP on comparison to patients who received OFA. However, the difference between percentages of MAP change recorded in patients of both groups was non-significant except at 30-min after insufflations.

These findings indicated proper control of OFA on surgical stimuli that may initiate pressor response and illustrated the feasibility of OFA as the sole anesthetic for various surgical procedures. In line of this assumption, Lavand'homme & Estebe [12] suggested that OFA stands as a new paradigm, which can deliver safe and stable anesthesia without intraoperative (IO) opioids to patients undergoing various surgical procedures. Also, Leas et al. [20] reported that opioid-free multimodal pain management is safe and effective option in patients undergoing shoulder arthroplasty with a very low risk of requiring rescue opioids and Soffin et al. [21] found OFA within an ERAS pathway for lumbar spinal decompression can minimize perioperative opioid exposure without adversely affecting pain control or recovery. Moreover, Mulier [22] documented that opioid-free general anesthesia is a viable option for gynecological and breast surgeries. Furthermore, Mulier & Dillemans [23] reported that OFA was associated with fewer complications and lower healthcare resource utilization for patients undergoing bariatric surgery.

The reported significant difference between the percentage of MAP change at 30-min after abdominal insufflations could be attributed to decreased MAP secondary to the hypotensive effect of remifentanil and not to exaggerated MAP in patients of OFA group. In line with this explanation, Bakan et al. [17] reported significantly higher frequency patients requiring ephedrine to treat hypotension in patients received remifentanil-based anesthesia compared to those received OFA. Recently, Grape et al. [24] in meta-analysis of studies compared IO remifentanil versus DEX and found rates of hypotension; shivering and postoperative nausea and vomiting (PONV) were twice as frequent in patients who received OFA.

Among 216 MAP readings, increased MAP measures by >20% of baseline measure was recorded in 10 (4.6%) versus 3 (1.4%) readings in OFA and OBA groups, respectively with a non-significant difference (p=0.091) between both groups. These findings illustrated the safety of OFA for laparoscopic surgery and the feasibility of this type of surgery under OFA. In support of this outcome, Díaz-Crespo et al. [25] presented a case scheduled for laparoscopic bariatric surgery who while maintaining OFA, was converted to open surgery with correct control achieved of both hemodynamics and perioperative pain. Recently, Frauenknecht et al. [26] documented that there is strong evidence that OBA does not reduce PO pain, but is associated with more PONV, when compared with OFA.

The reported beneficial effects of OFA could be attributed to varied effects of each of the used drugs; namely parecoxib sodium, dexmedetomidine and lidocaine, to induce and maintain OFA. Such attribution was in line with Guo et al. [27] who suggested that COX-2 inhibitor parecoxib exerts its analgesic effect on surgical pain through the inhibition of spinal cord neuronal extracellular signal-regulated kinase activation and Takaku et al. [28] experimentally found pretreatment with a single dose of parecoxib reduced the inflammatory response with attenuation of serum and tissue levels of IL-1α, IL-1β, IL-6, IL-10, & TNF-α.

Regarding, effects of DEX, Funai et al. [29] experimentally suggested that systemic α2-adrenoceptor stimulation by DEX may facilitate inhibitory synaptic responses in the superficial dorsal horn to produce analgesia mediated by activation of the pontospinal noradrenergic inhibitory system. Also, Yamakita et al. [30] experimentally, suggested that DEX has a peripheral mechanism of anti-inflammatory action through inhibition of p38 MAPK phosphorylation via TNF-α and this provides a molecular basis for its preventive action on peripheral sensitization following surgery. Clinically, Jebaraj et al. [31] documented that intraoperative DEX has equal analgesic efficacy to fentanyl and can be used as the sole analgesic agent in patients undergoing robotic urological surgery and Zhang et al. [32] found DEX infusion significantly decreased morphine consumption during the first 24-h PO with concomitant decreased plasma cortisol and IFN-γ/IL-10 levels, but increased percentages of CD8+ & CD4+/CD8+ cells, so Zhang et al. [32], attributed the effect of DEX infusion to its modulatory effect on stress reactions during the perioperative period. Recently, Grape et al. [24] in meta-analysis of studies

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compared IO remifentanil versus DEX and found pain scores at 2-hr PO were lower, time to analgesia request was longer and use of PO morphine were less with DEX.

Concerning lidocaine, Cui et al. [33] attributed antihyperalgesia effects of systemic lidocaine to inhibition of phosphorylation of Ca2+/calmodulin-dependent protein kinase II and protein expression levels in somatosensory cortical neurons. Also, Kurabe et al. [34] experimentally, attributed the analgesic action of IV lidocaine in acute pain to its inhibition of glutamate release from presynaptic terminals in spinal substantia gelatinosa neurons with concomitant hyper-polarization of postsynaptic neurons by shifting the membrane potential leading to decreased excitability of spinal dorsal horn neurons. Clinically, Nakhli et al. [35] found intravenous lidocaine infusion permitted a reduction of volatile anesthesia and IO opioid consumption during renal surgery, so it could provide effective strategy especially in low- and middle-income countries. Also, Soto et al. [36] reported that perioperative lidocaine infusion may be a useful analgesic adjunct in enhanced recovery protocols due to its immuno-modulatory properties over surgical stress and so suggested its use in the context of multimodal analgesia.

Conclusion

The applied protocol for OFA provided satisfactory IO analgesia and control of surgery-induced pressor reflexes. Also, it allowed reduction of PO analgesic consumption with early ambulation and reduced PONV that were reflected as shorter PO hospital stay. However, wider-scale comparative studies are mandatory to establish these outcomes.

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