EGYPTIAN JOURNAL OF ANAESTHESIA
2022, VOL. 38, NO. 1, 139–149
https://doi.org/10.1080/11101849.2022.2031547

Multimodal, non-opioid based analgesia for women presented for laparoscopic hysterectomy

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ABSTRACT

Objectives: Evaluation of outcome of women undergoing laparoscopic hysterectomy under general anesthesia with intraoperative (IO) multimodal analgesia.

Patients & Methods: 129 women were allocated into three groups: Group F received fentanyl loading dose and IO infusion; Group D received loading doses of dexmedetomidine (DEX) and lidocaine (LID) and infusions; Group M included patients received parecoxib sodium infusion (80 µg/ml), 30 minutes prior to induction of anesthesia and loading doses and IO infusions as group D in addition to parecoxib infusion. Heart rate (HR) and mean arterial pressure (MAP) were continuously non-invasively monitored. Blood samples were obtained for ELISA estimation of serum levels of inflammatory cytokines. Outcomes included adequacy of IO analgesia to control intraoperative MAP changes and postoperative (PO) pain scores and its relation to change in serum cytokines' levels.

Results: Fentanyl infusion induced significantly higher incidence and extent of decreased MAP in relation to preoperative MAP, while IO analgesia used for groups M and D allowed more hemodynamic stability. Patients of groups D and M had significantly shorter duration of PACU stay, longer duration of PO analgesia and lower number requests of rescue analgesia with significantly lower 24-hr pain score. Serum cytokines' levels were significantly lower in patients of group M than in groups D and F with significantly lower levels in patients of group D compared to group F.

Conclusion: Multimodal IO analgesia was efficient to provide IO hemodynamic stability, reduce PO pain, consumption of rescue analgesia and serum cytokines' levels.

ARTICLE HISTORY
Received 3 March 2020
Accepted 14 January 2022

KEYWORDS
Multimodal analgesia; intraoperative infusions; hemodynamic stability; inflammatory cytokines; postoperative pain

1. Introduction

Abnormal uterine bleeding (AUB) describes any variation from normal bleeding patterns in non-pregnant, reproductive-aged women lasting for at least 6 months [1]. AUB is a common condition that leads to increased health care costs and decreased quality of life [2]. Management of AUB involves both medical and surgical options [3], and hysterectomy offers a definitive surgical approach to AUB and is associated with high levels of patient satisfaction [4]. However, management of AUB must depend on a patient's fertility plans [3].

Inadequate postoperative (PO) pain management is a challenge for application of ambulatory surgery protocols [5]. Pain management with conventional opioids can be challenging due to dose-limiting adverse events [6], such as sedation, respiratory depression, and postoperative nausea and vomiting (PONV), which are the most common reasons for readmission after ambulatory surgery [5].

The effects of perioperative intravenous (IV) lidocaine (LID) are discrepant some trials found LID infusion has beneficial effects regarding PO pain with decreased opioid consumption, rapid restoration of bowel function and decreased hospital stay [7,8], while other trials found IV lidocaine was not able to reduce PO pain, opioid consumption, and duration of ileus or length of hospital stay [9].

Dexmedetomidine (DEX) is highly specific α2-adrenoceptor agonist with sedative, anxiolytic, analgesic and sympatholytic effects [10]. The potential advantages of neuroprotection and minimal impact on neuronal function [11], stable hemodynamics and potential myocardial and renal protection [12], opioid and anesthesia sparing effects, and minimal respiratory depression render DEX an effective anesthetic adjuvant [13].

Multimodal analgesic regimen using different techniques is the best approach for treating PO pain, maximizing analgesia and reducing side effects [14]. However, for ambulatory patients, multimodal

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analgesia must provide the best analgesic effect and patient satisfaction while respecting the rules of safety for ambulatory surgery [15].

1.1. Objectives

Evaluation of outcome of women undergoing laparoscopic hysterectomy under general anesthesia with intraoperative (IO) multimodal analgesia.

1.2. Settings

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1.3. Design

Prospective comparative clinical trial.

1.4. Patients & methods

This study was started since June 2018 after approval of the study protocol by the Local Ethical Committee. All women attending the outpatient clinic of gynecology department presenting by dysfunctional uterine bleeding (DUB) were eligible for evaluation by gynecologists and women assigned for hysterectomy were eligible for evaluation for enrolment in the current study. Exclusion criteria uterine pathologies that could be managed with uterus preserving surgeries, uterine pathologies that could not be managed laparoscopically, inflammatory disorders, maintenance on immunosuppressive drugs, diabetes mellitus, hypertension, hepatic or renal diseases. Women wishing to preserve their fertility and those refused to sign the consent for participation in the study were also excluded. Enrolment criteria multipara women presenting by DUB secondary to intrauterine pathology who were ASA I–III and signed the written fully informed consent that approved by the Local Hospital Authorities.

1.5. Randomization & grouping

Randomization relied on preparation of dark-sealed envelops containing cards carrying group label and were prepared by an assistant who was blinded about the significance of the symbol. Enrolled women were asked to choose one envelop and according to the label symbol were categorized into one of three groups.

Grouping was based on the regimen of IO analgesia to be used: Group F included patients who will receive fentanyl (FEN) infusion, Group D included patients who will receive dexmedetomidine (DEX) and lidocaine (LID) infusions and Group M included patients who will receive multimodal IO analgesia consists of DEX, LID and parecoxib sodium.

1.6. Preparation of the used drugs

Drugs that will be used for induction and IO analgesia were prepared by a clinical pharmacist who knows the card's label significance, while anesthetists in charge (authors) were blinded about both the card's label significance and drugs to be used.

(1) For induction of anesthesia, two syringes were prepared for each group

- In group F: G1.1 syringe contained fentanyl loading dose (2 µg/kg diluted to a total volume of 10 cc with normal saline) and G1.2 syringe contained 10 cc of normal saline as placebo.
- In group D & M: syringes labeled G2.1 and G3.1 contained DEX loading dose (0.6 µg/kg) and syringes G2.2 and G3.2 contained LID loading dose (1.5 mg/kg). Both DEX and LID were diluted to a total volume of 10 cc with normal saline.

(1) For IO analgesia, three infusion bottles were prepared

- In group F: G1.1 infusion was normal saline, G1.2 infusion was fentanyl infusion that was prepared to supply 0.3 µg/kg/hr and G1.3 infusion was normal saline.
- In group D: G2.1 infusion was normal saline, G2.2 infusion contained DEX prepared to supply 1 µg/kg/hr and G2.3 infusion contained LID and was prepared to supply 2 mg/kg/hr.
- In group M: G3.1 infusion contained 40 mg parecoxib sodium dissolved in 500 cc normal saline to provide 80 µg/ml and was started, according to the manufacturer's instructions, 30 minutes prior to induction of anesthesia to reach C_{max} of the drug, G3.2 infusion contained DEX prepared to supply 1 µg/kg/hr and G3.3 infusion contained LID and was prepared to supply 2 mg/kg/hr.

1.7. Anesthetic protocol

At pre-anesthetic room, baseline heart rate (HR) and mean arterial blood pressure (MAP) were determined non-invasively. Under complete aseptic conditions a 5-ml blood sample was obtained for assigned investigations and all patients received infusion bottles labeled G1.1, 2.1 and 3.1, 30 minutes preoperatively and was maintained during surgery. Patients were premedicated with IV midazolam (0.03 mg/kg) and were maintained well-oxygenated using oxygen 100% as 5 L/min flow rate.

Anesthesia was induced using propofol 2 mg/kg, drugs prepared for induction according to group-label and cis-atracurium 0.6 mg/kg. After tracheal

intubation, the lungs were ventilated with 100% O_2 in air using a semi-closed circle system for a tidal volume of 6–8 ml/kg, and the ventilatory rate was adjusted to maintain an end-tidal carbon dioxide ($paCO_2$) of 32–35 mmHg. Balanced anesthesia was maintained with sevoflurane MAC 1 in order to maintain MAP changes within ±20% of the preoperative measures and cis-atracurium supplemental doses were given according to patient's physiological reaction to surgical stimuli. IO analgesia was provided immediately after tracheal intubation using the prepared infusion bottles in addition to that started at the pre-anesthetic room. After abdominal desufflation, residual neuromuscular blockade was reversed with IV injection of neostigmine 0.05 mg/kg with atropine 0.02 mg/kg and patients were extubated. Infusions that had used for IO analgesia were stopped and patients were transferred to the post-anesthetic care unit (PACU). Throughout duration of surgery, patients were continuously non-invasively monitored for MAP and HR. At PACU, oxygen saturation was monitored using pulse oximetry and oxygen (6 L/min) was administrated via a face-mask 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 [16].

1.8. Postoperative care

(1) Duration of PO analgesia was determined as the time since PACU transfer till the 1st request of rescue analgesia.
(2) PO pain was assessed at time of PACU transfer and every 2 hours for 8-hr and every 4-hr till end of 24-hr PO using the numeric rating scale (NRS) with 0 indicates no pain and 10 indicates intolerable pain [17]. Rescue analgesia was provided on NRS score of ≥4 as an initial dose of parecoxib 40 mg IV, then 20 mg IV on request.

1.9. Study outcomes

(1) Adequacy of IO analgesia was defined as its ability to control MAP changes in reflex to surgical stress as judged by the extent of MAP changes during surgery in relation to preoperative MAP.
(2) Secondary outcomes included

- Time till fulfilling criteria for PACU discharge, frequency of requests of rescue analgesia, time till 1st ambulation, PO complications and PO hospital stay.
- The extent of change in serum levels of pro-inflammatory cytokines with nociceptive properties in relation to preoperative levels.

1.10. Blood sampling & investigations

Three blood samples were obtained at pre-anesthetic room and 6-hr and 24-hr PO. Blood samples (5 ml) were collected using aseptic technique [18], put in clean dry tube, allowed to clot and then serum was separated in clean dry Eppendorf tube to be stored at −80°C till assayed. Serum interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α) were measured using enzyme linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions and were read using a 96 well microplate ELISA reader (Dynatech MR 7000). Control blood samples (5 ml) were obtained from 10 of subjects attended blood bank for donation and had passed the pre-donation investigations.

1.11. Investigations

All investigations were performed by a clinical pathologist who was blinded about the clinical diagnosis.

(1) Serum IL-1β was measured with the enzyme linked immunoassay (ELISA) kit (catalogue no. MBS175901, MyBioSource, Inc., San Diego, USA) by quantitative sandwich enzyme immunoassay technique [19].
(2) Human IL-6 was measured with the enzyme linked immunoassay (ELISA) kit (catalogue no. IL631-k01, Eagle Biosciences, Inc., USA) by quantitative sandwich enzyme immunoassay technique [20].
(3) Human TNF-α was measured with the enzyme linked immunoassay (ELISA) kit (catalogue no. ab46087, abcam Inc., San Francisco, USA) by quantitative sandwich enzyme immunoassay technique [21].

2. Statistical analysis

Previous studies that examined 28 [22] or 32 [23] patients per group to evaluate hemodynamic differences between patients received LID versus magnesium sulphate IV infusion [22] or LID versus FEN or LID & FEN combination infusions [23], but reported non-significant difference between these groups. A sample size of 39 patients in each group was calculated to detect a 20% reduction in preoperative MAP with the use of studied IO infusions with a power of 85% and dropout of 5%. To guard against IO exclusion of some cases, the study was designed to include 43 patients per group. Obtained data were presented as mean ± SD, numbers, percentages and median. Results were analyzed using paired t-test for intra-group comparisons, One-way ANOVA Test for intergroup comparisons, Mann-Whitney test and Chi-square test (X^2 test) for non-parametric results. Statistical analysis was conducted using the IBM SPSS

(Version 23, 2015; IBM, South Wacker Drive, Chicago, USA) for Windows statistical package. P value <0.05 was considered statistically significant.

3. Results

The study included 142 women eligible for evaluation; 13 women were excluded and 129 women were randomly allocated into the three study groups (Figure 1). There was non-significant (p > 0.05) variance between enrolment data of studied patients, as shown in Table 1.

Pre-anesthetic medication significantly decreased MAP measurements in of all patients, but despite of the non-significant difference between the three groups the effect was more pronounced in patients of group M who received combined midazolam and parecoxib premedication. The used IO analgesia reduced the pressor reflexes to intubation and abdominal insufflations as evidenced by the significantly lower MAP measurements in comparison to preoperative MAP with non-significant differences between the three groups despite being lower in group F. At 30-min and 60-min after insufflations, mean MAP measurements were significantly lower in patients of group F compared to

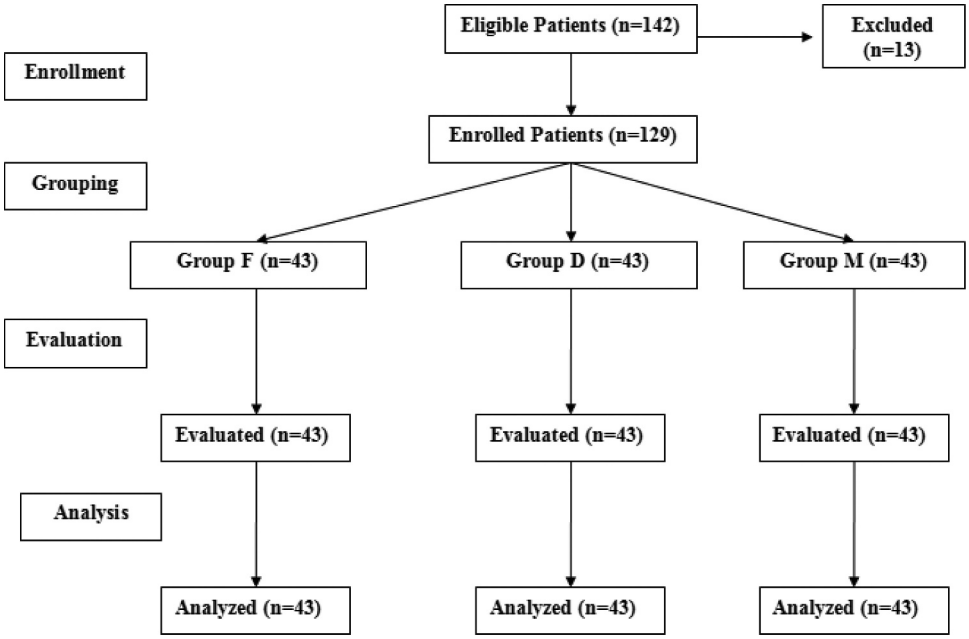

Figure 1. Flow chart of the study.

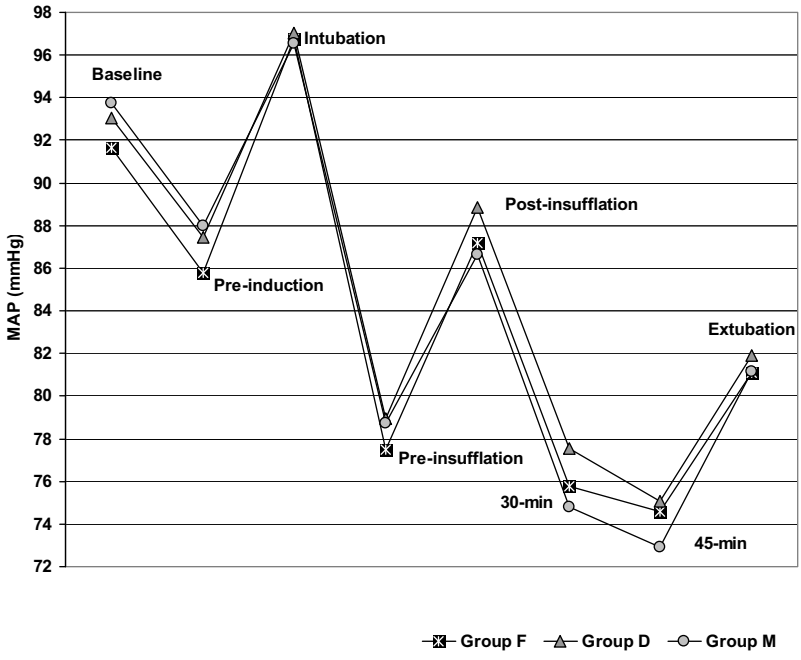

Figure 2. Mean MAP measurements compared to baseline MAP.

Table 1. Enrolment data of patients of studied groups.

Data		Group F	Group D	Group M	P value
Age (year)		46.2 ± 4.7	47.2 ± 5.6	46.5 ± 5	0.645
Parity		3.1 ± 0.9	3.3 ± 1.1	3.2 ± 1	0.735
Weight (kg)		87.7 ± 4.6	85.8 ± 6.6	88 ± 5.4	0.153
Height (cm)		169.7 ± 3.4	169.1 ± 3.6	170.2 ± 3.1	0.357
Body mass index (Kg/m^2)		30.5 ± 1.9	30 ± 2.1	30.4 ± 2.1	0.496
ASA grade	I	29 (67.4%)	27 (62.8%)	30 (69.8%)	0.971
	II	10 (23.3%)	11 (25.6%)	9 (20.9%)	
	III	4 (9.3%)	5 (11.6%)	4 (9.3%)	

Data are presented as mean ± SD; numbers & percentages; group F received fentanyl infusion; Group D received dexmedetomidine and lidocaine infusions; Group M received dexmedetomidine, lidocaine and parecoxib sodium infusions; P value indicates the significance of difference between studied groups; P value >0.05 indicates non-significant difference between studied groups

patients of group D, while were non-significantly lower in comparison to group M with non-significantly lower measures among patients of group M than in patients of group D. At time of extubation, mean MAP measurements of all patients were non-significantly lower compared to preoperative measurements with non-significant differences between studied groups (Table 2,Figure 2).

Prior to abdominal insufflations, 15 patients (11.6%) had decreased MAP measurements by ≥20% of preoperative measurements with non-significant difference between the three groups. At 30 min after insufflations, 43 patients (33.3%) had decreased MAP measurements by ≥20% of preoperative measurements with significantly (p = 0.0066) higher incidence in group F in comparison to group D and non-significantly (p = 0.078) higher incidence than in group M and non-significantly (p = 0.323) higher incidence in group M compared to group D. At 60 min after insufflations, 62 patients (48.1%) had decreased MAP measurements by ≥20% of preoperative measurements with significantly higher incidence in group F in comparison to groups D (p = 0.00056) and M (p = 0.0092) and non-significantly (p = 0.372) higher incidence in group M compared to group D (Figure 3).

Heart rate measurements showed variability during anesthesia time; in comparison to preoperative HR, pre-induction HR was significantly decreased, while at time of tracheal intubation HR was significantly increased in all patients with non-significant differences between the three groups, despite being lower with fentanyl.

Prior to abdominal insufflations, IO infusions significantly decreased HR in comparison to preoperative measurements with significantly lower rate in group F than in group D. In group M, HR change before insufflations was non-significantly higher than group F; but was non-significantly lower than group D. At time of abdominal insufflations, IO infusions non-significantly decreased HR measurements than preoperative measurements with non-significant difference between the three groups. At 30-min and 60-min after insufflations HR was significantly lower than preoperative HR in all patients with non-significant difference between the three groups, despite being lower in group F. Moreover, IO infusions controlled pressor reflexes to

Table 2. Mean MAP measurements during anesthesia time in the three groups.

Groups Time		Group F	Group D	Group M	P1 value	P2 value	P3 value
Preoperative		93.7 ± 5	93 ± 4.5	91.7 ± 5.1	0.497	0.061	0.188
Pre-induction		88 ± 6*	87.5 ± 6.2*	85.8 ± 5.5*	0.705	0.084	0.191
Intubation		96.5 ± 4.7*	97 ± 4.6*	96.8 ± 5.1*	0.628	0.843	0.792
Insufflations	Pre	78.7 ± 4.8*	79 ± 6*	77.5 ± 5.6*	0.836	0.281	0.245
	At	86.6 ± 5.4*	88.9 ± 5.1*	87.2 ± 5.5*	0.051	0.636	0.146
	30-min	74.8 ± 3.5*	77.6 ± 4.6*	75.8 ± 4.7*	0.0025	0.279	0.078
	60-min	72.9 ± 3*	75.1 ± 3.7*	74.6 ± 5*	0.0042	0.064	0.627
Extubation		81.1 ± 3.3*	81.9 ± 3.8*	81.1 ± 3.9*	0.334	0.945	0.337

Data are presented as mean ± SD, Group F included patients received IO fentanyl infusion, Group D included patients received dexmedetomidine & lidocaine IO infusions, Group M included patients received dexmedetomidine, lidocaine & parecoxib IO infusions; * indicates significance of difference in comparison to preoperative measurements, P1 indicates the significance of difference between groups F & D; P2 indicates the significance of difference between groups F & M; P3 indicates the significance of difference between groups D & M; P value >0.05 indicates non-significant difference; P value <0.05 indicates significant difference;

Table 3. HR measurements of patients of studied groups during anesthesia time.

Time		Group F	Group D	Group M	P1 value	P2 value	P3 value
Preoperative		83.2 ± 3.5	84.6 ± 2.8	83.5 ± 4.6	0.052	0.752	0.199
Pre-induction		76 ± 3.1*	77.3 ± 2.7*	77.5 ± 4.5*	0.053	0.071	0.746
Intubation		84.4 ± 4.1*	85.9 ± 3.3*	85.3 ± 2.8*	0.385	0.292	0.9
Insufflations	Pre	75.5 ± 2.3*	77.6 ± 3.2*	76.2 ± 3.9*	0.0009	0.321	0.079
	At	82.9 ± 3.1	83.9 ± 2.7	83 ± 4.2	0.135	0.793	0.129
	30-min	74 ± 2.8*	75.2 ± 3.4*	74.4 ± 4*	0.076	0.577	0.326
	60-min	72.7 ± 3.5*	73.6 ± 3.4*	73.1 ± 3.8*	0.251	0.618	0.533
Extubation		80.9 ± 3*	79.8 ± 3.6*	79.4 ± 4.1*	0.139	0.064	0.637

Data are presented as mean ± SD, Group F included patients received IO fentanyl infusion, Group D included patients received dexmedetomidine & lidocaine IO infusions, Group M included patients received dexmedetomidine, lidocaine & parecoxib IO infusions; * indicates significance of difference in comparison to preoperative measurements, P1 indicates the significance of difference between groups F & D; P2 indicates the significance of difference between groups F & M; P3 indicates the significance of difference between groups D &M; P value >0.05 indicates non-significant difference; P value <0.05 indicates significant difference

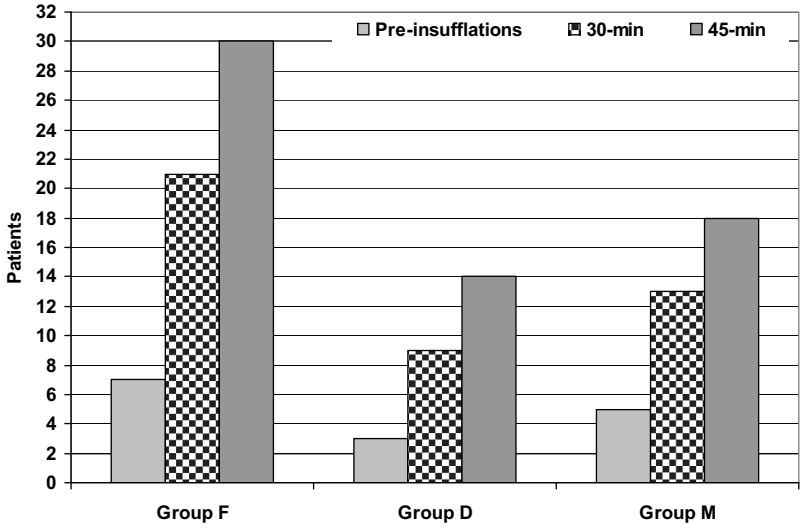

Figure 3. Number of patients developed IO decreased MAP by >20% of preoperative MAP.

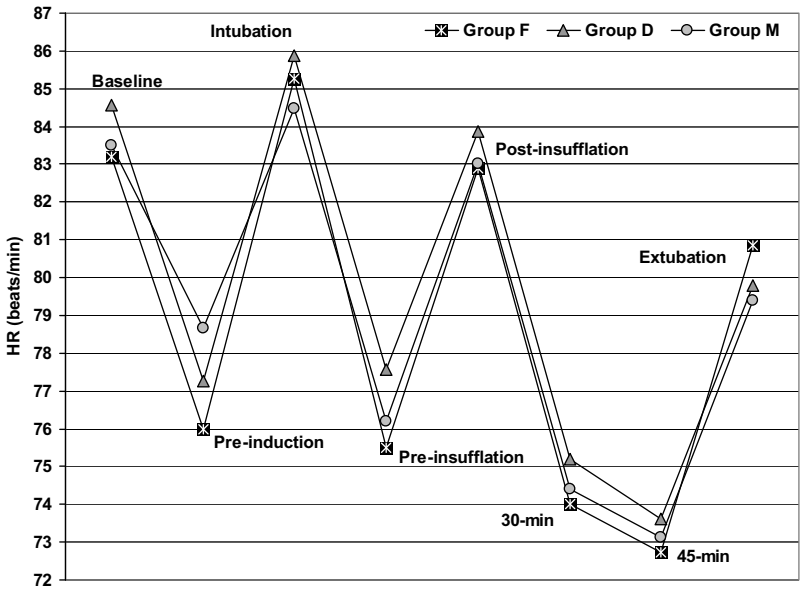

Figure 4. Mean HR measurements compared to baseline HR of patients of studied groups.

tracheal extubation, so that HR measurement were increased but were significantly lower compared to pre-operative measurements with non-significant difference between the three groups (Table 3,Figure 4).

Operative and anesthesia times showed non-significant differences between the study groups, while duration of PACU stay and time till 1st ambulation were significantly longer in group F than in other groups and were non-significantly shorter in group M than in group D. Eighty-eight patients required PO analgesia with significantly lower number of patients required PO analgesia among group M in comparison to groups D ($p = 0.024$) and M ($p = 0.043$) and non-significantly ($p = 0.802$) higher number among patients of group D than group F. However, among patients requested for rescue analgesia, time lapsed till 1st request of PO analgesia was significantly ($p < 0.00001$) shorter in group F in comparison to groups D and M with non-significantly longer duration in group M compared to group D. Similarly, cumulative NRS score during 24-hr PO was significantly higher in group F in comparison to group D ($p = 0.000015$) and group M ($p < 0.00001$). Determined PO pain NRS scores were significantly lower in patients of groups D & M in comparison to patients of group F till 8-hr PO with non-significant differences between groups D and M, but in favor of group M. At 16-hr PO, NRS pain scores were significantly lower in patients of group F in comparison to patients of groups D and M, but at 12-hr, 20-hr and 24-hr the differences were non-significant between the three groups despite being in favor of group M (Figure 5).

At time of PACU discharge, there was non-significant difference between patients of studied groups regarding sedation score, despite being higher in patients of group F. At 3-hr after PACU discharge,

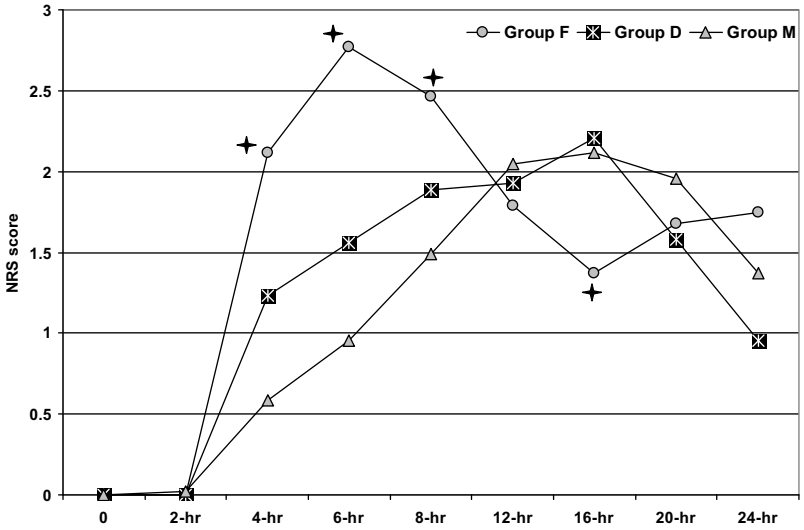

Figure 5. Mean NRS score of patients of studied groups determined during 24-hr PO (✦: significant difference versus D & M groups).

sedation score was significantly higher in patients of group F in comparison to groups D (p = 0.0074) and M (p = 0.0007) with non-significantly (p = 0.378) higher score of patients of group D than group M. Twenty-nine patients developed PO complications, 16 had PONV and 10 patients had low MAP, and 3 patients in group F developed mild itching. The incidence of PO complications was significantly (p = 0.024) higher in group F than group D and non-significantly (p = 0.088) higher than in group M with non-significant difference (p = 0.559) between groups D and M (Table 4).

Mean preoperative serum levels of total patients of IL-6 (2.4 ± 0.31 pg/ml), TNF-α (29.5 ± 7.8 pg/ml) and IL-1β (1.56 ± 0.48 pg/ml) were significantly higher in comparison to control subjects (1.17 ± 0.13; 12.44 ± 2.5 & 0.855 ± 0.2 pg/ml, respectively) with non-significant difference between studied groups. At 6-hr after surgery, serum cytokines' levels were significantly higher in all patients in comparison to preoperative level and in patients of group F in comparison to levels estimated in patients of groups D and M with non-significantly higher levels in patients of group D in comparison to group M. At 24-hr after surgery serum cytokines' levels were significantly lower in patients of group F in comparison to their respective 6-hr levels but were non-significantly lower compared to their preoperative levels. On contrary, serum cytokines' levels of patients of groups D and M were significantly lower in comparison to patients of group F and in comparison to their respective preoperative and 6-hr PO levels with significantly lower levels in patients of group M in comparison to patients of group D (Table 5). There was positive significant correlation between at 6-hr PO pain scores and serum cytokines' levels in groups D and M, while in group F the correlation was positive non-significant (Table 6).

4. Discussion

Intraoperative analgesic regimens used for patients of groups D and M allowed more MAP stability throughout anesthesia time than fentanyl infusion used for patients of group F as evidenced by the significantly higher incidence and extent of decreased MAP in relation to

Table 4. Operative and 24-hr PO data of patients of studied groups.

Time			Group F	Group D	Group M	P1 value	P2 value	P3 value
Operative time (min)			79.5 ± 11.8	82.5 ± 10.9	83.7 ± 10.7	0.222	0.085	0.597
Anesthesia time (min)			98.4 ± 12.1	95.4 ± 10.2	95.6 ± 10	0.235	0.241	0.951
PACU stay time (min)			23 ± 5.4	20.7 ± 4.8	19.7 ± 5.6	0.038	0.0069	0.401
Time till 1st ambulation (hr)			5.4 ± 1.2	4.5 ± 1.4	4.3 ± 1.3	0.001	0.00052	0.514
PO rescue analgesia	No of patients requested		32 (74.4%)	33 (76.7%)	23 (53.5%)	0.802	0.043	0.024
	Time till 1st request		9.4 ± 3.9	15 ± 5.3	16.75.1	<0.00001	<0.00001	0.204
Cumulative NRS pain score			1.55 ± 0.3	1.26 ± 0.28	1.17 ± 0.29	0.000015	<0.00001	0.153
PO analgesia-related complications	Sedation score	At PACU discharge	3.8 ± 0.7	3.5 ± 0.9	3.6 ± 0.8	0.219	0.244	0.894
		3-hr later	2 ± 1.1	1.5 ± 0.7	1.4 ± 0.5	0.0074	0.0007	0.378
	PONV		7 (16.3%)	4 (9.3%)	5 (11.6%)	0.024	0.088	0.559
	Itching		3 (7%)	0	0			
	Hypotension		5 (11.6%)	2 (4.7%)	3 (7%)			

Data are presented as mean ± SD, Group F included patients received IO fentanyl infusion, Group D included patients received dexmedetomidine & lidocaine IO infusions, Group M included patients received dexmedetomidine, lidocaine & parecoxib IO infusions; PO: Postoperative; PACU: Post-anesthetic care unit; PONV: Postoperative nausea & vomiting; P1 indicates the significance of difference between groups F & D; P2 indicates the significance of difference between groups F & M; P3 indicates the significance of difference between groups D &M; P value >0.05 indicates non-significant difference; P value <0.05 indicates significant difference

Table 5. Serum levels of cytokines estimated at 6-hr and 12-hr PO in patients of studied groups.

Group / Cytokine	Time	Group F	Group D	Group M	P1 value	P2 value	P3 value
IL-6 (pg/ml)	Preoperative	2.43 ± 0.27	2.5 ± 0.37	2.4 ± 0.31	0.418	0.721	0.271
	6-hr PO	3.17 ± 0.57*	2.87 ± 0.5*	2.78 ± 0.3*	0.012	0.00026	0.402
	24-hr PO	2.33 ± 0.35†	2.1 ± 0.26*†	1.89 ± 0.27*†	0.0009	0.000088	0.00048
TNF-α (pg/ml)	Preoperative	32 ± 7.2	33.2 ± 9.8	29.5 ± 7.8	0.527	0.191	0.055
	6-hr PO	39.9 ± 9.7*	35.4 ± 7.5*	33.1 ± 11.6*	0.017	0.004	0.289
	24-hr PO	29.5 ± 6.2†*	26.6 ± 4.3*†	24.4 ± 5.11*†	0.013	0.00007	0.034
IL-1β (pg/ml)	Preoperative	1.658 ± 0.8	1.581 ± 0.7	1.557 ± 0.48	0.632	0.474	0.852
	6-hr PO	2.385 ± 0.624*	2.067 ± 0.68*	1.938 ± 0.55*	0.027	0.0007	0.337
	24-hr PO	1.55 ± 0.48†	1.269 ± 0.30*†	1.14 ± 0.27*†	0.002	0.00015	0.047

Data are presented as mean ± SD, Group F included patients received IO fentanyl infusion, Group D included patients received dexmedetomidine & lidocaine IO infusions, Group M included patients received dexmedetomidine, lidocaine & parecoxib IO infusions; * indicates significance of difference in comparison to preoperative estimates, † indicates significance of difference in comparison to 6-hr estimates; P1 indicates the significance of difference between groups F & D; P2 indicates the significance of difference between groups F & M; P3 indicates the significance of difference between groups D &M; P value >0.05 indicates non-significant difference; P value <0.05 indicates significant difference

Table 6. Pearson's correlation between pain score and serum cytokines' levels at 6-hr PO in studied groups.

		Group F	Group D	Group M
IL-6 (pg/ml)	r	0.127	0.310	0.443
	p	0.401	0.043	0.003
TNF-α (pg/ml)	r	0.106	0.331	0.534
	p	0.497	0.030	0.0009
IL-1β (pg/ml)	r	0.159	0.357	0.378
	p	0.309	0.019	0.013

Group F included patients received IO fentanyl infusion, Group D included patients received dexmedetomidine & lidocaine IO infusions, Group M included patients received dexmedetomidine, lidocaine & parecoxib IO infusions; r: Pearson's correlation coefficient; p indicates the significance of the correlation coefficient; p value >0.05 indicates non-significant difference; p value <0.05 indicates significant difference

preoperative MAP in group F in comparison to other groups. Moreover, analgesic infusions used for patients of groups D and M provided more HR stability than fentanyl infusion and could control the pressor reflexes to intubation, abdominal insufflations and extubation as favorably as fentanyl as evidenced by the non-significant differences between mean MAP and HR measurements between the three groups at these times.

These results point to the possibility of control of pressor reflexes using non-opioid analgesia and such effect could be maximized by the use of multimodal analgesia. These findings and assumption support that previously reported in literature evaluated the use of opioid-free analgesia (OFA) during various surgical procedures and concluded that OFA can deliver safe and stable anesthesia without IO opioids to patients undergoing various surgical procedures [24–27].

Patients of groups D and M had more favorable PO outcome than those of group F as manifested by the significantly shorter duration of PACU stay and time till 1st ambulation, longer duration of PO analgesia and lower number of patients' required PO analgesia. Moreover, cumulative 24-hr NRS score was significantly lower in patients of groups D and M than patients of group F. However, patients of group M required rescue analgesia significantly less than patients of group D.

These results are in line with that previously reported in literature, where **Leas et al**. [28] reported that perioperative opioid-free multimodal pain management is safe and effective option in surgical patients with a very low risk of requiring rescue opioids. Also, **Bello et al**. [29] found OFA reduces anesthetic consumption, early PO pain scores and requirement for morphine titration after thoracotomy. **Mujukian et al**. [30] documented that multimodal analgesia incorporating peri-operative opioid-sparing agents is an effective method for reducing perioperative opioid utilization and pain after minimally invasive colorectal surgery. Recently, incorporation of regional blocks, as erector spinae plane block [31] and superior hypogastric plexus block [32], as a part of multimodal analgesia was found to increase its efficacy with decreased consumption and cost of inhaled agents and opioids in the perioperative period.

Preoperative serum cytokines' levels were significantly higher compared to control group; a finding supported that previously reported in literature [33–35] indicating the systemic inflammatory stress response to the presence of intra-uterine pathology. Moreover, serum levels, estimated 6-hr after surgery, were significantly higher than preoperative levels; another finding indicated the impact of surgery, even laparoscopic surgery on inflammatory milieu. This finding goes in hand with previous literature that documented increased pro-inflammatory cytokines levels in response to surgery, either open [36] or laparoscopic [37] but was lessened by laparoscopic [37,38] or endoscopic surgery [39].

Interestingly, serum levels of pro-inflammatory cytokines estimated in samples obtained 6-hr after surgery were significantly lower in patients of groups M and D in comparison to patients of group F with non-significantly lower levels with multimodal analgesia. These findings point to a possible anti-inflammatory action of drugs used in group D in addition to the anti-inflammatory effect of parecoxib used in group M. In support of this assumption, at 24-hr PO, serum cytokines' levels were significantly lower than preoperative levels in all patients but were significantly lower in patients of group M than in patients of groups D and F and in patients of group D than those in group F.

These results go in hand with **Guo et al**. [40] prospectively documented that anesthesia with DEX during radical surgery for lung cancer can effectively reduce the

inflammatory response of the lungs and protect its function. **Deng et al**. [41] reported significantly lower incidence rates of SIRS after percutaneous nephrolithotomy lithotripsy on perioperative application of DEX and attributed this decrease to inhibition of inflammatory responses reflected as lower serum levels of IL-6 and TNF-α. Recently, **Yang et al**. [42] out of a meta-analysis found perioperative DEX treatment significantly decreased IL-6 and TNF-α compared to saline. Also, **Liu et al**. [43] found serum TNF-α and IL-6 levels, in women had laparoscopic surgery for ovarian cancer, were significantly lower in patients received DEX than those received midazolam and continuous use of DEX during general anesthesia effectively reduced the perioperative serum levels of TNF-α and IL-6.

Additionally, there was positive significant correlation between NRS pain scores, and number of requests of rescue analgesia and serum cytokine's levels. This finding could attribute the reported superior outcome of IO infusions used for groups D and M to the decreased serum levels of cytokines with nociceptive effect and assure the anti-inflammatory effect of these drugs. In support of this assumption, experimentally, **Yamakita et al**. [44] attributed the preventive action of DEX on peripheral sensitization following surgery to its peripheral anti-inflammatory action through inhibition of p38 MAPK phosphorylation via TNF-α and **Takaku et al**. [45] found single dose pretreatment with parecoxib reduced the inflammatory response to surgery with attenuation of serum and tissue levels of IL-1β, IL-6 and TNF-α, and **Soto et al**. [46] clinically found lidocaine infusion provided analgesia due to its immuno-modulatory properties over surgical stress and so suggested its use in the context of multimodal analgesia.

5. Conclusion

Multimodal IO analgesia is effective regimen for women undergoing laparoscopic hysterectomy, provides stable hemodynamics, control pro-inflammatory cytokines and decrease PO pain scores, requirements for rescue analgesia and opioid-related side effects.

6. Limitation

The trial was limited by being a single center study, so multicenter studies are advocated to establish the obtained results especially for the anti-inflammatory effects of the used drugs.

Acknowledgments

The authors acknowledge the staff members of Obstetrics & Gynecology Department at Tanta University Hospital.

Disclosure statement

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

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