Original Research Article

Dexmedetomidine, Ketamine and Lidocaine Infusion for Prevention of Postoperative Nausea and Vomiting in Laparoscopic Gynecological Surgery: Randomized Trial

Abstract

Background: The intraoperative use of large bolus doses or continuous infusions of potent opioids may be associated with increased analgesic consumption postoperatively. In ambulatory surgery, opioid related side effects, such as postoperative nausea and vomiting (PONV), prolonged sedation, ileus and urinary retention may delay recovery and discharge or cause unanticipated hospital readmission. The aim was to evaluate the effect of opioid sparing technique via infusion of dexmedetomidine, ketamine and lidocaine on post-operative nausea and vomiting in laparoscopic gynecological surgery.

Methods: A total of 80 patients were randomly allocated into 2 groups, 40 patients each. Control group (group c) received fentanyl while, Study group (group S) received infusion of a mixture of dexmedetomidine, ketamine and lidocaine. The PONV impact scale, intraoperative consumption of isoflurane and fentanyl and post operative 24 hr. morphine consumption were measured.

Results: 18 (45%) patients of control group experienced PONV versus 7 (17.5%) patients of study group and it was clinically significant. Clinically significant vomiting was observed in10 (25%) patients of control group and 1 (2.5%) patient of study group. There was a marked reduction in fentanyl, isoflurane and 24 hours' morphine consumption in group S compared to group C.

Conclusion: Opioid sparing anesthesia with dexmedetomidine, ketamine and lidocaine infusion are superior to fentanyl for prevention of post-operative nausea and vomiting and reduction of isoflurane and, fentanyl consumption and provides better patient satisfaction in laparoscopic gynecological surgery.

Keywords: Dexmedetomidine, ketamine, lidocaine, postoperative nausea and vomiting, laparoscopic surgery.

Introduction

Opioids have a widespread usage for perioperative analgesia. However, there may be an association between increased postoperative analgesic consumption and the continuous usage or the administration of large doses. In ambulatory surgery, adverse events of opioid such as postoperative nausea and vomiting (PONV), ileus, urinary retention and over sedations may result in delayed recovery and hospital discharge [1].

The incidence of PONV in day care surgeries, vary from 8% to 45 % [1]. PONV are distressing symptoms, commonly occur after surgeries under general anesthesia as laparoscopy, laparotomy, ear, nose, and throat (ENT), neurological, breast and gynecological surgeries[2]. The pathogenesis of PONV is very complex and the triggering inputs may arrive from multiple areas. There are independent causal factors for PONV such as Laparoscopic surgery, bowel obstruction, female gender, younger age group, longer operations, obese patients, no smoking, PONV history, motion sickness, and postoperative opioid therapy [3.]

The postoperative pain of gynecological laparoscopic surgery is complicated and an increasing evidence of controlling it by opioid-free and multimodal for acceleration of recovery [4].

PONV and postoperative pain are still frequent after laparoscopic gynecological surgery despite the use of multimodal analgesia, which are composed of non-steroidal anti-inflammatory drugs, dexamethasone, opioids, and local anesthetics.[5]

So, we hypothesized that the infusion consisting of lidocaine, dexmedetomidine and ketamine, as alternative to opioids, may be a feasible anesthetic technique for laparoscopic gynecological surgery and may have less incidence of PONV and lower opioid requirements in the early postoperative period.

The aim of this study was to assess the effect of infusion of dexmedetomidine, ketamine and lidocaine as an opioid sparing anesthetic technique on PONV in laparoscopic gynecological surgery. The primary outcome was the incidence of PONV. The secondary outcomes were measurement of intraoperative isoflurane and fentanyl consumption and postoperative 24 h morphine consumption.

Methods

This randomized prospective double-blinded study was conducted at Tanta University Hospital from December 2019 to August 2020. The protocol of trial was approved from Ethical Committee of Faculty of Medicine Tanta University with approval code (33362/9/19) and registered on clinical trials.gov with ID: NCT04706897 and Patients' written informed consent was taken from every patient.

The study included female patients aged 21-60 years of age with ASA physical status I or II scheduled for elective laparoscopic gynecological surgery. Patients have a body mass index >35 kg/ m^2, pregnant, breast-feeding women, hepatic, renal or cardiac insufficiency, diabetes mellitus, alcohol or drug abuse, psychiatric disease, history of chronic pain, allergy or contraindication to any of the study drugs were excluded from the study.

The sample size calculation was performed using Epi-Info 2002 software statistical package designed by World Health Organization (WHO) and by centers for Disease Control and Prevention (CDC). The sample size was calculated as N≥ 36 in each group based on the following consideration: 95% confidence limit and 80% power of the study, group ratio 1:1 and expected decrease of the incidence of PONV from 45% in control group to 15% in study group according to a previous study [(6)]. Four cases were added to each group to overcome dropouts so, forty patients in each group were allocated for intervention.

Randomization was done before induction of anesthesia using computer generated random numbers and opaque sealed envelopes were used to indicate group assignment. The anesthesiologist, who prepared the study medications and opened the envelopes in the sequence to reveal the treatment allocation, was not involved in perioperative data collection or anesthetic management of the patients. The anesthesiologist who collected the data, the anesthesiologist concerned with intraoperative management and the person who performed the statistical analysis were blind. Moreover, the patients were unaware of their group assignment.

After arrival to OR standard monitors were connected to the patient and all patients received 2 mg midazolam IV and 4 mg dexamethasone IV for PONV prophylaxis

Two sets of syringes were prepared**:** the first set for group C (control group); 50 ml infusion pump syringe (A) containing normal saline instead of mixture in study group, and 10 ml syringe (C) containing 100 µg fentanyl. The second set for group S (study group); 50 ml infusion pump syringe (B) containing the study mixture [a mixture of dexmedetomidine (2 µg/ml), ketamine (0.5 mg /ml) and lidocaine (4 mg /ml) [5], and 10 ml syringe (D) containing normal saline (instead of fentanyl in the control group set).

For both groups: infusion of the 50 ml syringe (containing normal saline or study mixture according to group allocation) was started at rate of 0.2 ml/ kg/hr. for ten min before induction and was continued till head-down position, peritoneal insufflation and placement of abdominal ports are complete. Anesthesia was induced with 2 mg/kg ideal body weight (IBW) of propofol, and 0.5 mg/kg IBW atracurium was used for intubation. O_2 flow was 1L/min. for closed circuit ventilation, and isoflurane was used for maintenance of anesthesia at end tidal concentration to keep entropy within the range of 40-60. If entropy gets more than 60, isoflurane concentration was increased till 1.5 MAC, if entropy remained more than 60 for 3 min, 50 µg fentanyl was given (by another syringe) and the rescue fentanyl was recorded. At the end of surgery, complete

reversal of neuromuscular blockade was performed using 0.05 mg/kg neostigmine and 0.01 mg/kg atropine IV [5]. Both groups received: paracetamol (1gm /6 h. IV infusion) and diclofenac sodium (75 mg /12 h. IM) starting at the end of the surgery before recovery from anesthesia and preoperative wound infiltration with 5 ml of 0.25% bupivacaine were injected at each incisional area (four sites, total of 20 ml) [6].

Measurements: The primary outcome was PONV incidence that was assessed using the simplified PONV impact scale [7]. Patients were asked to rate the impact of nausea on their functional status and daily activities such as dressing, hygiene and walking. The response options were: not at all = (0) at the scale, sometimes = (1), often or most of the time = (2), and all of the time = (3). In addition, the vomiting count was used to quantify vomiting intensity, scored as the number of vomits where, no vomit = 0 at the scale, 1 vomit = 1, 2 vomits = 2 and three or more vomits = 3. Both scores were added together to obtain the simplified PONV impact scale score and clinically important PONV was defined as a total score of ≥ 5

Other measurements included demographic data and patient characteristics as age (years), BMI (kg/ m^2), ASA physical status and duration of surgery (min). Intraoperative isoflurane (ml), fentanyl (µg) and first 24 h. morphine consumption (mg) were also recorded.

Morphine was given for postoperative pain relief according to visual analogue sale (VAS). If VAS was more than 3, intravenous morphine titration was administered as a bolus of 2 mg (body weight ≤60 kg) or 3 mg (body weight >60 kg) with 5-min lockout interval between each bolus and repeated till pain is relieved. Pain relief is defined as a VAS of 3 or lower [8]. VAS was measured at 0.5, 2, 4, 8, 12, 18 and 24 h. postoperatively.

Patient satisfaction using a 5–point scale, 1 for (very satisfied), 2 for (somewhat satisfied), 3 for (neither satisfied nor dissatisfied), 4 for somewhat dissatisfied and 5 for very dissatisfied [9].

Statistical analysis

Organization and analysis of data were performed using SPSS version 26. (IBM®, Chicago, IL, USA). Normality of data distribution was checked by the Shapiro-Wilks test and the histogram visualization. Parametric variables with normal distribution (e.g. mean arterial pressure) were expressed as mean ± standard deviation and analyzed using unpaired Student's T-test for comparison between the two groups and repeated measures ANOVA analysis for comparison within the same group. Non-parametric variables (e.g. VAS) score and the parameters which didn't follow the normal distributions (e.g. total postoperative morphine consumption) were expressed as median and interquartile range (IQR) and analyzed using Mann-Whitney (U) test for comparison between the two groups and Friedman test with post hoc Wilcoxon test for comparison within the same group. Categorical data values were expressed as number percent and were analyzed using Chi-square test or Fisher exact test as appropriate. A two tailed P value < 0.05 was considered statistically significant.

Results

In the present study, 117 patients were assessed for eligibility, 37 patients were excluded; of them 31 patients did not meet the inclusion criteria [ASA more than II (n=6), body mass index more than 35 kg/m^2 (n=8), breast feeding women (n=5), hepatic, renal, or cardiac insufficiency (n=4), diabetic patient (n=3), history of chronic pain (n=3), psychiatric disease (n=2)], and 6

patients refused to participate in the study. The remaining 80 patients were randomly allocated into two groups in a parallel way (40 patients in each one); group C (control group): non-opioid sparing anesthesia with fentanyl and, group S (study group): opioid sparing anesthesia with dexmedetomidine, lidocaine and ketamine**.** All the 80 patients were followed-up and their data were statistically analyzed (fig.1)

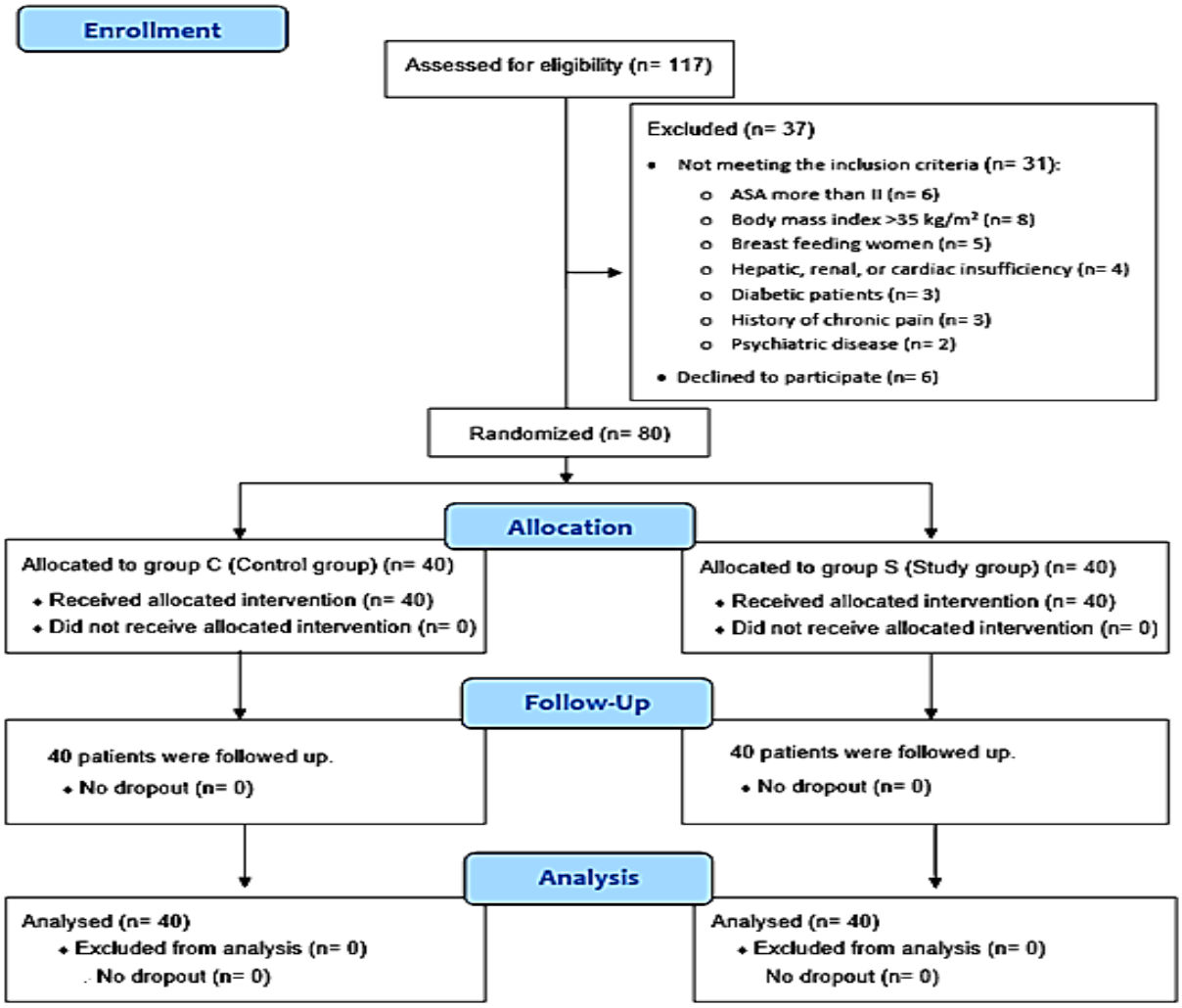

Figure 1: Participant flow diagram.

Regarding the demographic data: age, BMI, ASA physical status and duration of surgery, the two groups were comparable ($p > 0.05$) (table 1).

Table 1: Demographic data and patient characteristics in the two studied groups.

	Group C (n = 40)	Group S (n = 40)	P value
Age (years)	34 ± 8	36 ± 9	0.292
BMI (kg/m^2)	27 ± 4	27 ± 3	0.648

ASA physical status [n (%)]			0.478
ASA I	25 (62.5%)	28 (70%)	
ASA II	15 (37.5%)	12 (30%)	
Duration of surgery (min)	90 ± 15	83 ± 18	0.066
Baseline heart rate (beats /min)	78 ± 8	78 ± 7	0.763
Baseline mean arterial blood pressure (mmHg)	92 ± 9	90 ± 8	0.329

Data presented as mean ± SD except for ASA physical status which is presented as number (%), There was no statistical difference between groups at P value < 0.05, BMI: body mass index, ASA: American Society of Anesthesiologists (ASA) physical status classification system

The incidence of PONV (p value 0.008), Simplified PONV impact scale score (p value 0.017) and clinically significant vomiting (p value 0.007) were significantly decreased in group S than group C (table 2).

Table 2: PONV and other complications in both groups

	Group C (n = 40)	Group S (n = 40)	P value
PONV [n (%)]	18 (45%)	7 (17.5%)	00.008*
Simplified PONV impact scale score [Median (IQR)]	0 (0-4.25)	0 (0-0)	00.017*
Clinically significant vomiting [n (%)]	10 (25%)	1 (2.5%)	00.007*
Hypotension [n (%)]	4 (10%)	7 17.5%)	00.518
Bradycardia [n (%)]	4 (10%)	7 17.5%)	00.518

*significant as P value <0.05, Data presented as number (%) except for Simplified PONV impact scale score which is presented as median (interquartile range), PONV: post operative nausea and vomiting

There was a significant reduction in intraoperative isoflurane consumption (mL), (p value <0.001), number of patients who needed intraoperative fentanyl (p value 0.002) and 24 h. morphine consumption (p value <0.001) in group S compared to group C. However, the first time to request analgesia (h) was shorter in group S compared to group C with p value <0.001, (table 3), and VAS at 1 h was significantly increased in group S than group C (P <0.001), (fig.2)

Table 3: Intraoperative isoflurane (ml), fentanyl (µg), 24 h. morphine (mg) consumption and first time to request analgesia (h) in both groups.

		Group C (n= 40)	Group S (n =4 0)	P value
Isoflurane consumption (mL)	Median (IQR)	15 (15-17)	13 (13-13)	**<0.001***
intraoperative fentanyl consumption (µg)	Median (IQR)	100 (77.5-130)	0 (0-0)	**<0.001***
Patients who needed intraoperative fentanyl	n (%)	20 (50%)	7 (17.5%)	**0.002***
24 h morphine consumption (mg)	Median (IQR)	7.5 (6-9)	6 (6-6.75)	**<0.001***
First time to request	Median (IQR)	3 (2-3)	1(1-2)	**<0.001***

analgesia (h)				

*: significant as p value < 0.05, Data presented as median (interquartile range) except for patients who needed intraoperative fentanyl which is presented as number (%), Data were compared by Mann-Whitney (U) test
*significant as P value <0.05

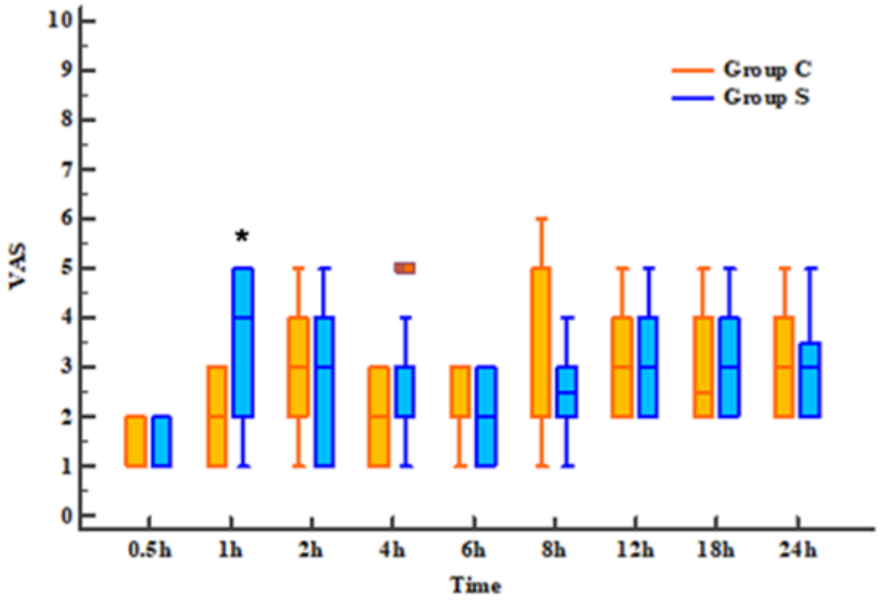

Fig 2: Visual analogue score (VAS) changes in the two studied groups

Regarding Patients' satisfaction between the two studied groups it was better in group S compared to group C (P value: 0.019) (fig.3)

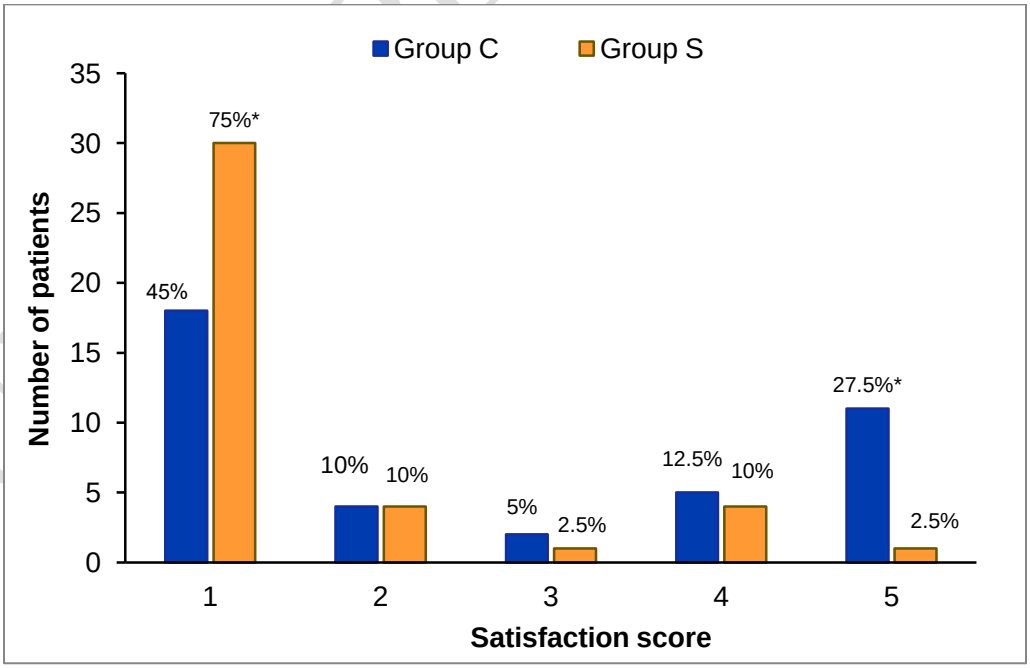

Fig 3: Patient satisfaction in the two studied groups

Discussion

The PONV and PONV impact scale were significantly lower in group S than group C. Also, PONV and clinically significant vomiting were significantly lower in group S than group C. This could be attributed to the effect of the study infusion mixture containing dexmedetomidine, ketamine and lidocaine.

Dexmedetomidine succeeded in prevention of PONV as dexmedetomidine spares opioids and inhaled anesthetics. Dexmedetomidine also decreases nor-adrenergic activity through decreasing sympathetic outflow or stimulating α2 presynaptic in the locus coeruleus which may be related to PONV. Additionally, it may have a direct antiemetic property [10].

The study infusion mixture also contains lidocaine which result in the reduction in the incidence of PONV. Lidocaine prevents PONV by opioid use reduction, hemodynamic stability maintenance in the perioperative stage, postoperative pain reduction and promotion of early recovery of the gastrointestinal tract. Moreover, ketamine is an N-Methyl-D-aspartate receptor antagonist and has analgesic and anti-inflammatory effects [11].

Bakan et al., 2015 were in line with our findings as they concluded that in patients with a high risk of PONV, opioid-free anesthesia with lidocaine, dexmedetomidine, and propofol infusions may be used during laparoscopic cholecystectomy [12].

Also, Li et al., found that dexmedetomidine (0.5 g/kg) decreased PONV in pediatric strabismus surgeries without increasing times of extubation or recovery [13].

Also, the study of Liang et al. 2015, found that intravenous dexmedetomidine infusion may reduce PONV incidence compared to placebo and opioids which was probably due to the lower intraoperative opioids consumption. In addition, Lin et al., 2009, concluded that the dexmedetomidine addition to IV PCA morphine resulted in less morphine-induced nausea [14].

Moreover, Wang et al. 2019, reported that PONV incidence was significantly less in lidocaine group compared to control group [15].

As regards, intraoperative isoflurane consumption and intraoperative fentanyl consumption; both of them decreased significantly in group S compared to group C. This may be due to the composition of the study mixture, which contained dexmedetomidine, lidocaine and ketamine, all of them had analgesic properties and so, decreased the need for both inhalational agents and opioids. Moreover, Sridhar et al., 2015 [16]. found that lidocaine attenuated the levels of c-reactive protein, interleukin-6 and total leukocytic count in the immediate postoperative period. These inflammatory mediators are related to stress of surgery and pain. By attenuating these mediators, lidocaine can offer pain relief and reduce opioid consumption. Also, Wang et al., 2019 found that lidocaine group showed a significant reduction in the total dose of remifentanil [15].

With respect to post-operative morphine consumption and visual analogue score (VAS) in the first 24h in our study, the morphine consumption was significantly decreased in group S compared to group C even though patients needed morphine earlier in group S. This early requirement can be explained by stoppage of infusion at study group at the end of the operation and not extended in the postoperative period.

Bakan et al., 2015 [12] agreed with our results when they demonstrated that lower postoperative fentanyl requirements would be related to total intravenous anesthesia compared to opioid based anesthesia.

Moreover, Brinck et al 2018 [17] reached a conclusion that pain intensity and postoperative analgesic consumption may be decreased by perioperative intravenous ketamine.

Also, Sridhar et al., 2015 [16]. found that postoperative morphine requirement and postoperative pain scores at each time point revealed a significant decrease in lidocaine group than saline group.

Against our results, Grady et al 2012 [18] who reported that adding ketamine or lidocaine did not affect postoperative opioid consumption. And Wuethrich et al 2012 [19] who found that opioid consumption after kidney surgery is not affected by perioperative administration of systemic lidocaine over 24 hours. This could be explained on the basis that, in those studies the authors used lidocaine infusion at doses different from those used in the present study.

Limitations of the study: We didn't assess the level of sedation in the post-operative period and, we didn't report the recovery time. Also, sample size was relatively small and may need further studies with increasing sample size. More randomized trials need to be conducted to verify the findings of our study.

Conclusion

Opioid sparing anesthesia with dexmedetomidine, ketamine and lidocaine infusion is superior to fentanyl for prevention of PONV and reduction of isoflurane and, fentanyl consumption and provides better patient satisfaction in laparoscopic gynecological surgery.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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