Effect of intravenous lidocaine combined with dexmedetomidine on postoperative nausea and vomiting after laparoscopic total hysterectomy

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Abstract
Background
A few studies have manifested that intravenous (IV) lidocaine or dexmedetomidine decreased the incidence of postoperative nausea and vomiting (PONV). We investigated whether lidocaine plus dexmedetomidine infusion could better reduce the incidence of PONV than placebo after laparoscopic total hysterectomy.

Methods
This prospective, randomized controlled study enrolled 126 women undergoing elective laparoscopic total hysterectomy with general anesthesia. They divided into the following two groups: patients in the lidocaine combined with dexmedetomidine group (group LD) received lidocaine (1.5 mg/kg loading, 1.5 mg/kg/h infusion) and dexmedetomidine (0.5 μg/kg loading, 0.4 μg/kg/h infusion), respectively. Patients in the control group (group CON) received the equal volume of saline. The primary outcome was the incidence of nausea, vomiting and PONV for the first 48 hours after surgery. The secondary outcomes included intraoperative propofol and remifentanil consumption, postoperative fentanyl requirement, Ramsay sedation score, and the incidence of bradycardia during post-anesthesia care unit (PACU) stay period.

Results
Data of 59 in CON and 60 in LD groups were analyzed. The incidence of nausea, vomiting, and PONV in group LD during the 0 to 2 hours and 24 to 48 hours after the operation was slightly lower than group CON, but the difference was not statistically significant between the two groups. The incidence of nausea, vomiting, and PONV was much lower in group LD than group CON at 2 to 24 hours after surgery (P<0.05, P<0.01, P<0.01, respectively). The cumulative requirement of fentanyl during the first 48 hours after surgery was significantly reduced in group LD compared to group CON (P<0.01, P<0.01, P<0.05, respectively).
respectively). Propofol and remifentanil total dose in the intraoperative period was significantly lower in group LD compared with group CON (P<0.01 and P<0.01). However, the level of sedation and incidence of bradycardia during the PACU stay period were markedly increased in group LD compared with group CON (P<0.01 and P<0.01).

Conclusion

Lidocaine plus dexmedetomidine infusion markedly decreased the occurrence of nausea, vomiting and PONV within the 2 to 24 hours after laparoscopic total hysterectomy with general anesthesia. However, it increased the incidence of bradycardia and the level of sedation during the PACU stay period.

Background

Nausea and vomiting after surgery is one of unpleasant, trouble, and the most common side effects with general anesthesia, especially use of a large amount of opioids. Despite the advances in surgical techniques, anesthetic, and management of anesthesia, PONV, as well as postoperative pain, are very crucial problem for anesthesiologists and surgeons after surgery. With the development of enhanced recovery after surgery (ERAS), laparoscopic surgery is widely used for gynecological patients because of some advantages, including postoperative pain relief, accelerated recovery after surgery, and an improved cosmetic effect [1]. However, subjects undergoing gynecological laparoscopic surgery are high-risk factors of PONV. It was reported that the incidence of PONV in high-risk patients with no prophylaxis was likely to reach up to 70% to 80% [2, 3, 4]. The occurrence of nausea and vomiting after surgery may result in more discomfort and dissatisfaction for patients, disorder of electrolyte, and prolonged the time of hospitalization. Currently, although a large amount of prophylactic measures are also effective in women. However, given the higher baseline risk, such as gynecological laparoscopic surgery, a single prophylactic measure is often not sufficient to achieve a
satisfactory PONV prophylaxis.

Dexmedetomidine is a highly selectively alpha 2-adrenergic agonist, which has been described as having sedation, anxiolysis, analgesia, and much less respiratory depression. As an anesthetic adjuvant, it has been widely used during the anesthesia period because of several benefit effects, such as reducing catecholamine release [5], sparing-opioids [6] and improving the quality of recovery [7, 8]. It was revealed that systemic administration of dexmedetomidine may enhance the analgesic effect of opioids and reduce opioids requirement during the perioperative and postoperative period [9, 10], and reduction of opioids consumption and requirement during the intraoperative and postoperative period may result in decreasing of opioid-related adverse reactions including PONV. Recently, some studies have pointed that perioperative dexmedetomidine administration could reduce the incidence of PONV [11, 12]. Additionly, a lot of studies showed that IV lidocaine has some beneficial effects, such as analgesic, anti-hyperalgesic, and anti-inflammatory properties [13, 14]. Recent meta-analysis showed that the perioperative lidocaine administration reduced risk of nausea but not vomiting overall during the first 48 hours after the operation [15]. Therefore, we hypothesized that the combination of lidocaine and dexmedetomidine would further reduce the incidence of nausea, vomiting, and PONV after laparoscopic total hysterectomy compared to placebo. The primary purpose of the present study was to examine the effect of a combined application of dexmedetomidine plus lidocaine on nausea, vomiting, and PONV within 48 hours after laparoscopic total hysterectomy undergoing general anesthesia.

Methods

The Ethics Committee of the Affiliated Anqing Hospital of Anhui Medical University (Ethics Committee reference number: AQ042) approved the present study. This prospective, randomized controlled study was registered at www.clinicaltrial.gov (NCT03788018). The
The present study was conducted from January 2018 to December 2018 at the Affiliated Anqing Hospital of Anhui Medical University. Patients were required to sign the informed consent at least one day before surgery. 126 patients with American Society of Anesthesiologists (ASA) physical status I and II, 40-55 years of age, and scheduled for elective laparoscopic total hysterectomy undergoing general anesthesia were enrolled. The exclusion criteria in the current study included preoperative atrioventricular block and bradycardia, history of allergy to local anesthetics, severe respiratory disease, impaired kidney or liver function. In addition, history of preoperative opioids medication and psychiatric were excluded from this study.

**Assigned groups and randomization**

Patients were randomized by a nurse of PACU independent of the study who obtained random numbers (random numbers generated by a computer), and patient allocation ratio was 1:1. Assignments were concealed in sealed envelopes. Patients were allocated into two groups, including group LD and group CON. Patients received IV bolus infusion of lidocaine (2%) 1.5 mg/kg and dexmedetomidine 0.5 µg/kg diluted with normal saline to 20 ml in group LD, respectively, over 10 minutes before induction of anesthesia, followed by a continuous IV infusion at rate of lidocaine 1.5 mg/kg [16] and dexmedetomidine 0.4 µg/kg [17] made up to 20 mL every hour until 30 min before the end of operation, respectively. Patients received 20 ml normal saline and 20 ml normal saline in group CON, respectively, over 10 minutes before induction of anesthesia, followed by a continuous IV infusion 20 ml normal saline and 20 ml normal saline every hour until 30 min before the end of surgery, respectively. Investigators, clinicians and patients were all fully blinded to treatment allocation. The drug solutions were prepared by an anesthesiologist who was not participated in the administration of the trial.

**Anesthesia protocol**
All surgical procedures for laparoscopic total hysterectomy were implemented by two high-experienced surgeons. All patients received intramuscular phenobarbital (0.1 g) 30 minutes before surgery. Basic non-invasive arterial pressure (NIBP), heart rate (HR), electrocardiogram (ECG), end-tidal CO₂ (PetCO₂), peripheral pulse oximeter (SPO₂), train-of-four (TOF), and Bispectral Index (BIS) monitors were attached to all the subjects for monitoring the vital sign, neuromuscular block, and the depth of anesthesia. Arriving at the operation room, patients were received the ringer’s lactate (1 mL/kg/h) to maintain its patency. All the patients were preoxygenated with 100% oxygen via facemask for 3 to 5 minutes before induction of anesthesia to obtain sufficient oxygenation. Anesthesia was induced with target-controlled infusion (TCI) of propofol and remifentanil. The target predicted plasma concentration of propofol was 3.0 μg/mL [18]. This predicted plasma propofol concentration was kept stable for 3 minutes and then remifentanil TCI begun. The target predicted plasma concentration of remifentanil was 5.0 ng/ml [19]. Cis-atracurium 0.15 mg/kg was injected intravenously when the patients lost consciousness, and an endotracheal tube (ETT) with an internal diameter of 6.5 mm (female) was inserted into the trachea after adequate muscle relaxation. Mechanical ventilation was performed using fabius machine. Tidal volume was set 6-8 mL/kg, and respiratory rate was set 10-13 beat/min (bpm) to keep the PetCO₂ between 35 and 45 mmHg during the intraoperative period. A supplemental dose of cis-atracurium was administered intermittently to maintain muscle relaxation during the anesthesia period. The depth of anesthesia was maintained by adjusting predicted propofol and remifentanil TCI according to BIS values and hemodynamic variables within 20% of preoperative values. BIS was kept between 45 and 60 during the anesthesia period. The ringer’s lactate solution was infused at a rate of 6-8 mL/kg/h during the intraoperative period. 30 minutes before the end of surgery, Fentanyl 1μg/kg was administered intravenously, and then patients were connected to an IV
patient-controlled analgesic system (IVPCA) with 0.3 µg/kg/h fentanyl and granisetron hydrochloride 6 mg (100 ml of total volume) to deliver a bolus of 0.075 µg/kg of the above analgesics with a lockout time of 15 minutes. Atropine (0.5 mg) and neostigmine (1 mg) was given by intravenously to reverse neuromuscular block when the patients restored spontaneous respiration. Patients were extubated when TOF ratio at least 0.9. The patients were transported to the PACU after their endotracheal tube were extubated in the operating room to continue treatment. All patients were continued to observe for 2 hours during the PACU stay period. The Ramsay sedation score and incidence of bradycardia during the PACU stay period were recorded. The operations were performed by two high-experienced surgeon under a CO$_2$ pneumoperitoneum, and the pressure of pneumoperitoneum was kept between 10 mmHg and 12mmHg for all patients. At the end of surgery, 10 mL of 0.75% ropivacaine was injected the abdominal trocar sites by one surgeon for providing wound infiltration analgesia after surgery.

**Outcomes variables**

Our primary outcome was the incidence of nausea, vomiting and PONV during the first 48 hours after surgery. The secondary outcomes included Ramsay sedation score, the incidence of bradycardia, postoperative cumulative fentanyl requirement, and propofol and remifentanil total dose during the anesthesia period. The intensity of pain after the operation was estimated with a 10-cm VAS in the PACU and the ward (0 for no pain, 10 for the most imaginable pain). If the VAS>3, an additional 25 µg of fentanyl was treated intravenously until the VAS<3. Sedation levels of subjects during the PACU stay period were evaluated with the Ramsay sedation scale (1: agitated and uncomfortable, 2: cooperative and orientated, 3: can follow simple directions, 4: asleep but strong response to stimulation, 5: asleep and slow response to stimulation and 6: asleep and no response to stimulation).
Sample size calculation

According to Geng ZY [20] study, a sample size of 58 patients per group was needed to confirm a 50% reduction in the incidence of PONV with a power of 80% and a significance level of 0.05. Therefore, we enrolled 126 cases to account for drop outs in the present study.

Statistical Analysis

All the statistical analyses in the present study were performed using SPSS statistics v.17 (IBM Corp., Armonk, NY, USA) software. Data are presented as the number (percentage) of subjects or mean±standard deviation. Categorical data were analyzed using the $\chi^2$ test or the Fisher’s exact test as appropriate. Continuous data in the two groups were analyzed using the independent t-test. A $P$ value of less than 0.05 was considered statistically significant.

Results

Of 140 patients screened for eligibility, 140 subjects for study were recruited and 126 patients were randomized in the current study. Among the 126 enrolled in the study, 7 subjects were excluded from the analysis: three patients were converted to open surgery; four patients turned off the analgesic pump because of postoperative drastic vomiting. Eventually, 59 patients in group CON and 60 patients in group LD were analyzed (Figure 1).

There were no significant differences between the two groups with respect to age, BMI, blood loss, intraoperative fluid infusion volume, duration of anesthesia, duration of surgery, history of smoking, history of PONV, and history of motion sickness (Table 1). Propofol and remifentanil total dose was much lower in group LD compared with group CON during the intraoperative period ($P<0.01$ and $P<0.01$). The level of sedation was
significantly higher during the PACU stay period in group LD compared to group CON ($P \leq 0.01$). The incidence of bradycardia was much higher in group LD than group CON during the PACU stay period ($P \leq 0.01$). But, severe bradycardia (heart rate [HR] <40 bpm) was not happen in group LD. The cumulative requirement of fentanyl during the first 48 hours after surgery was significantly reduced in group LD compared to group CON ($P \leq 0.01$, $P \leq 0.01$, $P \leq 0.05$, respectively). Extubation time was longer in group LD than group CON ($P \leq 0.01$) (Table 2).

The incidence of nausea, vomiting and PONV during the 0 to 2 hours after surgery was slightly lower in group LD than group CON ($P=0.634$, $P=0.619$, $P=0.439$, respectively), but this difference was not statistically significant between the group LD and group CON. The occurrence of nausea, vomiting and PONV within 2 to 24 hours after the operation was significantly decreased in group LD compared with group CON ($P \leq 0.05$, $P \leq 0.01$, $P \leq 0.01$, respectively). The incidence of nausea, vomiting and PONV at 24 to 48 hours after surgery was also not significant differences between the two groups ($P=0.311$, $P=0.369$, $P=0.429$, respectively) (Table 3).

Discussion

This trial demonstrated that IV lidocaine combined with dexmedetomidine markedly reduced the incidence of nausea, vomiting and PONV within the postoperative 2 to 24 hours compared to placebo after laparoscopic total hysterectomy with general anesthesia. However, the statistical difference was not observed for the occurrence of nausea, vomiting, and PONV between the 0 to 2 hours and 24 to 48 hours after surgery in group LD and group CON.

Several measures have been attempted to decrease the incidence of nausea, vomiting and PONV, but they were not able to completely eliminate it. Ahn E et al. indicated that lidocaine administration was significantly lower incidence of nausea compared with the
control group with laparoscopic colectomy, it most likely attributed to intravenous lidocaine decreased the total amount of fentanyl [21]. Samimi S et al. revealed that lidocaine 1.5mg/kg bolus intravenously 30 minutes before incision and constant rate infusion of lidocaine 2mg/kg/h until 1 hour after the end of procedure decreased the incidence of PONV [22]. However, the incidence of vomiting was not significant difference between treatment group and control group. The results of the meta-analysis by Weibel S et al. showed that IV lidocaine administration reduced nausea compared with control group during the perioperative period [15]. Additionally, Bielka K et al. found that dexmedetomidine infusion at rate of 0.5 μg/kg/h from induction of anaesthesia to extubation was reduced the incidence of PONV in patients after laparoscopic cholecystectomy (OR 5, 95% CI 1.1-26, p=0.005) [23]. Meta-analyses of clinical trials had similar results, that is, dexmedetomidine infusion during the anesthesia period decreased the incidence of PONV [24]. Suzuki T et al. have revealed that patients who were received dexmedetomidine administration had much lower incidence of PONV than those who were received NLA [25]. Geng ZY et al. also revealed that intraoperative dexmedetomidine infusion reduced the incidence of nausea early postoperative period but not vomiting in patients who received gynaecological laparoscopic surgery with general anesthesia [20]. In a study by Bakan M et al. showed that intravenous lidocaine and dexmedetomidine infusion for laparoscopic cholecystectomy reduced the incidence of PONV undergoing patients requiring tracheal intubation for general anesthesia [26]. In our study, we observed that lidocaine plus dexmedetomidine infusion significantly reduced the incidence of nausea, vomiting and PONV during the first 2 to 24 hours after surgery undergoing laparoscopic total hysterectomy with general anesthesia. Several identified independent risk factors for PONV for instance female, history of smoking, history of motion sickness or PONV, and laparoscopic surgery especially gynecological laparoscopic surgery in the
current study were not comparable significance between the two groups. The incidence of nausea, vomiting and PONV during the initial 2 to 24 hours after surgery was markedly lower in group LD compared with group CON. It may be associated with lidocaine plus dexmedetomidine administration had much less intraoperative remifentanil requirement, postoperative fentanyl consumption, and pain intensity during the first 2 to 24 hours after surgery. Moreover, Postoperative pain relief also might be decrease catecholamine release. Because high level of catecholamine in serum may be induce PONV. In the present study, our results were explained by several reasons. First, dexmedetomidine had sympatholytic and opioid-sparing effects, which reduced catecholamine concentrations and opioid consumption. Second, lidocaine plus dexmedetomidine infusion could provide better pain relief after surgery, and significantly decrease postoperative fentanyl consumption. This was similar results by Xu et al. who found that lidocaine combined with dexmedetomidine infusion resulted in greater analgesic and opioid-sparing effects compared to lidocaine and dexmedetomidine infusion alone in patients undergoing abdominal hysterectomy [27]. Third, lidocaine combined with dexmedetomidine administration probably much better inhibited stress response by intubation, operation, and pneumoperitoneum, which may be associated with lower catecholamine concentrations. Finally, we speculated that lidocaine combined with dexmedetomidine infusion might be have better anti-inflammatory effect. Although dexmedetomidine possess the hypnotic and sedative effect, bradycardia was the most common side effect of dexmedetomidine administration, especially a large dose of dexmedetomidine. Therefore, we chose a relatively lower dose (0.5 µg/kg loading, 0.4 µg/kg/h infusion) for decreasing the incidence of bradycardia and facilitating recovery after the operation. In our study, severe bradycardia was not observed during the combined infusion of lidocaine plus dexmedetomidine. Lidocaine constant rate infusion (CRI) is associated with sedation [28].
The results of our study demonstrated that the incidence of bradycardia and level of sedation were much higher in group LD than group CON during the PACU stay period. Meanwhile, we also found that lidocaine combined with dexmedetomidine infusion prolonged extubation time after surgery. Hence, lidocaine plus dexmedetomidine infusion reduced the incidence of nausea, vomiting and PONV, but increased the incidence of bradycardia and level of sedation during the PACU stay period, and prolonged extubation time.

Our study has several limitations. On the one hand, our sample was relatively small, and we were also not compared effects of intravenous lidocaine, dexmedetomidine alone on the incidence of nausea, vomiting and the overall incidence of PONV. On the other hand, although we speculated that combined application of lidocaine plus dexmedetomidine further inhibited stress response and inflammatory response, we were not detected levels of catecholamine and inflammatory factor such as IL-1, IL-6, and TNF-α in serum.

Conclusions

Lidocaine combined with dexmedetomidine administration may be provide better reduction of nausea, vomiting and PONV for the first 2 to 24 hours after the operation in patients undergoing laparoscopic total hysterectomy requiring tracheal intubation for propofol and remifentanil total intravenous anesthesia (TIVA). However, it increased the incidence of bradycardia and level of sedation during the PACU stay period.

Abbreviations

**IV**: Intravenous  **PONV**: Postoperative nausea and vomiting  
**PACU**: Post-anesthesia care unit  **ASA**: American Society of Anesthesiologists  
**ERAS**: Enhanced recovery after surgery  **NIBP**: Non-invasive arterial pressure  
**HR**: Heart rate  **ECG**: Electrocardiogram
**PetCO₂**: End-tidal CO₂  **SPO₂**: Peripheral pulse oximeter

**TOF**: Train-of-four  **BIS**: Bispectral Index  **TCI**: Target-controlled infusion

**ETT**: Endotracheal tube  **IVPCA**: IV patient-controlled analgesic system

**CRI**: Constant rate infusion  **TIVA**: Total intravenous anesthesia

**IL**: Interleukin  **TNF-α**: Tumor necrosis factor

Declarations

**Ethics approval and consent to participate**

This study and its protocol were approved by the ethics Committee of the Affiliated Anqing Hospital of Anhui Medical University (Ethics Committee reference number: AQ042). Written informed consent was obtained from all patients.

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets generated and/or analyzed during the current study are available from corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

No funding was received.

**Authors’ contributions**

SQX, XJ, SBW, and YHL conceived of the study and drafted the study protocol. SQX, XJ, SBW, SHH, and QL all participate in the study design and coordination of the study. SQX, XJ, and SHH contribute to data collection. SBW is the principal investigator and has overall responsibility for the study. SQX, XJ performed the statistical analysis for the study.
protocol. SQX, XJ and SBW draft and revised the manuscript. SQX, XJ, SBW and YHL critically revised the manuscript. All authors have read and approved the final manuscript.

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Not applicable

**References**

1. Aarts JW, Nieboer TE, Johnson N, Tavender E, Garry R, Mol BW, et al. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database Syst Rev 2015; 8:CD003677.

2. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, Zernak C, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 2004; 350: 2441-51

3. Wu O, Belo SE, Koutsoukos G. Additive antiemetic efficacy of prophylactic ondansetron with droperidol in out-patient gynecological laparoscopy. Can J Anaesth 2000; 47 (6):529-36.

4. Bhakta P, Ghosh BR, Singh U, Govind PS, Gupta A, Kapoor KS, Honkavaara P, et al. Incidence of postoperative nausea and vomiting following gynecological laparoscopy: A comparison of standard anesthetic technique and propofol infusion. Acta Anaesthesiol Taiwan 2016; 54(4):108-13.

5. Chen Y, Feng X, Hu X, Sha J, Li B, Zhang H, et al. Dexmedetomidine Ameliorates Acute Stress-Induced Kidney Injury by Attenuating Oxidative Stress and Apoptosis through Inhibition of the ROS/JNK Signaling Pathway. Oxid Med Cell Longev 2018; 2018:4035310.

6. Peng K, Zhang J, Meng XW, Liu HY, Ji FH. Optimization of Postoperative Intravenous Patient-Controlled Analgesia with Opioid-Dexmedetomidine Combinations: An Updated Meta-Analysis with Trial Sequential Analysis of Randomized Controlled
Trials. Pain Physician 2017; 20(7):569-96.

7. Shin HW, Yoo HN, Kim DH, Lee H, Shin HJ, Lee HW. Preanesthetic dexmedetomidine 1μg/kg single infusion is a simple, easy, and economic adjuvant for general anesthesia. Korean J Anesthesiol 2013; 65 (2):114-20.

8. Bekker A, Haile M, Kline R, Didehvar S, Babu R, Martiniuk F, et al. The effect of intraoperative infusion of dexmedetomidine on the quality of recovery after major spinal surgery. J Neurosurg Anesthesiol 2013; 25 (1):16-24.

9. Schnabel A, Meyer-Frießem CH, Reichl SU, Zahn PK, Pogatzki-Zahn EM. Is intraoperative dexmedetomidine a new option for postoperative pain treatment? A meta-analysis of randomized controlled trials. Pain 2013; 154 (7):1140-49.

10. Gómez-Vázquez ME, Hernández-Salazar E, Hernández-Jiménez A, Pérez-Sánchez A, Zepeda-López VA, Salazar-Páramo M. Clinical analgesic efficacy and side effects of dexmedetomidine in the early postoperative period after arthroscopic knee surgery. J Clin Anesth 2007; 19 (8):576-82.

11. Choi EK, Seo Y, Lim DG, Park S. Postoperative nausea and vomiting after thyroidectomy: a comparison between dexmedetomidine and remifentanil as part of balanced anesthesia. Korean J Anesthesiol 2017; 70 (3):299-304.

12. Ziemann-Gimmel P, Goldfarb AA, Koppman J, Marema RT. Opioid-free total intravenous anaesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis. Br J Anaesth 2014; 112(5):906-11.

13. Caracas HC, Maciel JV, Martins PM, de Souza MM, Maia LC. The use of lidocaine as an anti-inflammatory substance: a systematic review. J Dent 2009; 37 (2):93-7.

14. Hollmann MW, Durieux Me. Local anesthetics and the inflammatory response: a new therapeutic indication? Anesthesiology 2000; 93 (3):858-75.

15. Weibel S, Jelting Y, Pace NL, Helf A, Eberhart LH, Hahnenkamp K, et al. Continuous
intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. Cochrane Database Syst Rev 2018; 6:CD009642.

16. Kang JG, Kim MH, Kim EH, Lee SH. Intraoperative intravenous lidocaine reduces hospital length of stay following open gastrectomy for stomach cancer in men. J Clin Anesth 2012; 24 (6):465-70.

17. Wang T, Ge S, Xiong W, Zhou P, cang J, Xue Z. Effects of different loading doses of dexmedetomidine on bispectral index under stepwise propofol target-controlled infusion. Pharmacology 2013; 91 (1-2):1-6.

18. Oji M, Terao Y, Toyoda T, Kuriyama T, Miura K, Fukusaki M, et al. Differential effects of propofol and sevoflurane on QT interval during anesthetic induction. J clin Monit Comput 2013; 27 (3):243-48.

19. Kim EJ, shin SW, Kim TK, Yoon JU, Byeon GJ, Kim HJ. The median effective effect-site concentration of remifentanil for minimizing the cardiovascular changes to endotracheal intubation during desflurane anesthesia in pediatric patients. Korean J Anesthesiol 2012; 63 (4):314-20

20. Geng ZY, Liu YF, Wang SS, Wang DX. Intra-operative dexmedetomidine reduces early postoperative nausea but not vomiting in adult patients after gynaecological laparoscopic surgery: A randomised controlled trial. Eur J Anaesthesiol 2016; 33 (10):761-66.

21. Ahn E, Kang H, Choi GJ, Park YH, Yang SY, Kim BG, et al. Intravenous Lidocaine for Effective Pain Relief After a Laparoscopic Colectomy: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study. Int Surg 2015; 100 (3): 394-401.

22. Samimi S, Taheri A, Davari Tanha F. Comparison between intraperitoneal and intravenous lidocaine for postoperative analgesia after elective abdominal hysterectomy, a double-blind placebo controlled study. J Family Reprod Health 2015;
23. Bielka K, Kuchyn I, Babych V, Martycshenko K, Inozemtsev O. Dexmedetomidine infusion as an analgesic adjuvant during laparoscopic cholecystectomy: a randomized controlled study. BMC Anesthesiol 2018; 18 (1):44.

24. Jin S, Liang DD, Chen C, Zhang M, Wang J. Dexmedetomidine prevent postoperative nausea and vomiting on patients during general anesthesia: A PRISMA-compliant meta-analysis of randomized controlled trials. Medicine (Baltimore) 2017; 96 (1):e5770.

25. Suzuki T, Inokuchi R, Hanaoka K, Suka M, Yanagisawa H. Dexmedetomidine use during epiduroscopy reduces fentanyl use and postoperative nausea and vomiting: A single-center retrospective study. SAGE Open Med 2018; 6:2050312118756804.

26. Bakan M, Umutoglu T, Topuz U, Uysal H, Bayram M, Kadioglu H, et al. Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double-blinded study. Braz J Anesthesiol 2015; 65(3):191-99.

27. Xu SQ, Li YH, Wang SB, Hu SH, Ju X, Xiao JB. Effects of intravenous lidocaine, dexmedetomidine and their combination on postoperative pain and bowel function recovery after abdominal hysterectomy. Minerva Anestesiol 2017; 83(7):685-94.

28. Tsai TY, Chang SK, Chou PY, Yeh LS. Comparison of postoperative effects between lidocaine infusion, meloxicam, and their combination in dogs undergoing ovariohysterectomy. Vet Anaesth Analg 2013; 40 (6):615-22.

Tables

Table 1  Demographic baseline characteristics of the study group patients
| factor                        | Group CON (59) | Group LD (60) | P value |
|------------------------------|----------------|---------------|---------|
| Age (years)                  | 45.8±3.6       | 46±3.7        | 0.356   |
| BMI (kg/m²)                  | 22.3±1.2       | 22.4±1.1      | 0.433   |
| Blood loss (ml)              | 73.5±18.7      | 71.3±15.3     | 0.478   |
| Intra-operative fluid infusion (ml) | 896.2±154.1   | 926.8±177.3   | 0.318   |
| Duration of anesthesia (min) | 134.1±11.8     | 134.7±12.3    | 0.775   |
| Duration of surgery (min)    | 111.2±9.0      | 114.0±11.8    | 0.152   |
| History of smoking           | 7(12%)         | 10(17%)       | 0.454   |
| History of PONV              | 5(8%)          | 7(12%)        | 0.334   |
| History of motion sickness   | 8(14%)         | 6(10%)        | 0.569   |

Values are in mean ± SD, number, number (%).

Abbreviations: BMI, body mass index; PONV, postoperative nausea and vomiting; CON, control; LD, lidocaine plus dexmedetomidine.

Table 2  Clinical baseline characteristics of the study group patients
| Factor                          | Group CON (59) | Group LD (60) | P value       |
|--------------------------------|----------------|---------------|---------------|
| Propofol total dose (mg)       | 689.7±50.3     | 585.5±35.5a   | P0.001        |
| Remifentanil total dose (microg) | 1186.3±78.2   | 739.9±63.6a   | P0.001        |
| Dexmedetomidine total dose (microg) | NA        | 104.6±7.9     | NA            |
| Lidocaine total dose (mg)      | NA            | 268.2±26.0    | NA            |
| Extubation time (min)          | 6.2±1.3       | 7.5±1.3a      | P0.001        |

### Adverse events in the PACU

| Event                        | Group CON (59) | Group LD (60) | P value |
|------------------------------|----------------|---------------|---------|
| Bradycardia                  | 7 (12%)        | 34 (57%)a     | P0.001  |
| Rasmay sedation score (≥3)  | 6 (10%)        | 40 (67%)a     | P0.001  |

### Total fentanyl consumption

| Time Interval | Group CON (59) | Group LD (60) | P value |
|---------------|----------------|---------------|---------|
| 0 to 2 h      | 130.2±10.2     | 90.7±6.5a     | P0.001  |
| 2 to 24 h     | 497.2±29.4     | 476.1±37.4a   | P=0.001 |
| 24 to 48 h    | 902.9±51.0     | 878.2±55.9a   | P=0.013 |

Values are in mean ± SD, number (%).

Abbreviations: PACU, post-anesthesia care unit; CON, control; LD, lidocaine plus dexmedetomidine.
aP0.05 compared to group CON

Table 3  Comparison of postoperative nausea and vomiting outcomes of the study group patients

| Factors  | Group CON (59) | Group LD (60) | P value |
|----------|----------------|---------------|---------|
| Nausea   |                |               |         |
| 0 to 2 h | 3 (5%)         | 2 (3%)        | 0.634   |
| 2 to 24 h| 38 (64%)       | 22 (37%)a     | 0.03    |
| 24 to 48 h| 19 (32%)   | 14 (23%)      | 0.311   |
| Vomiting |                |               |         |
| 0 to 2 h | 2 (3%)         | 1 (2%)        | 0.619   |
| 2 to 24 h| 33 (56%)       | 17 (28%)a     | 0.003   |
| 24 to 48 h| 14 (24%)   | 10 (17%)      | 0.369   |
| PONV     |                |               |         |
| 0 to 2 h | 4 (7%)         | 2 (3%)        | 0.439   |
| 2 to 24 h| 41 (69%)       | 24 (40%)a     | 0.002   |
| 24 to 48 h| 20 (34%)   | 16 (27%)      | 0.429   |

Values are in mean ± SD, number (%).

Abbreviations: PONV, postoperative nausea and vomiting; CON, control; LD, lidocaine plus dexmedetomidine. aSignificantly difference from group CON.

aP0.05 compared to group CON

Figures
**Figure 1**

CONSORT flow diagram for the study.

**Supplementary Files**

This is a list of supplementary files associated with the primary manuscript. Click to download.
