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Comparison of dexmedetomidine and dexamethasone for prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy

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Background: Postoperative nausea and vomiting (PONV) are common following laparoscopic cholecystectomy (LC). Dexamethasone has been reported to reduce PONV. However, there is insufficient evidence regarding the effect of dexmedetomidine in decreasing PONV. This study was designed to compare the effects of a single dose of dexmedetomidine to dexamethasone for reducing PONV after LC.

Methods: Eighty-six adult patients scheduled for LC were randomized to receive either single dose 1 μg/kg of dexmedetomidine (Dexmed group, N = 43) or 8 mg dexamethasone (Dexa group, N = 43) before skin incision. During the first 24 h postoperatively, the incidence and severity of PONV were assessed. Pain and sedation scores were assessed on arrival in the recovery room and early postoperatively. Analgesic and antiemetic consumption during the 24 h after surgery were calculated. Intra-operative and postoperative hemodynamics were recorded.

Results: Twenty-one percent of the patients in the Dexmed group developed PONV compared to 28% in the Dexa group (P = 0.6). Severity of PONV was similar between the two groups (P = 0.07). Early postoperatively, pain severity was significantly lower in the Dexmed group, but sedation scores were significantly higher. The first analgesic request was significantly delayed in the Dexmed group (P = 0.02). The total amounts of intraoperative fentanyl and postoperative tramadol administered were significantly lower in the Dexmed group. No difference in ondansetron was noted between the two groups. Mean arterial pressure and heart rate were significantly lower in the Dexmed group after administration of dexmedetomidine. No major side effects were reported.

Conclusions: Dexmedetomidine reduces the incidence and severity of PONV, similar to dexamethasone. It is superior to dexamethasone in reducing postoperative pain and total analgesic consumption during the first 24 h after LC.

Key Words: Cholecystectomy, Dexamethasone, Dexmedetomidine, Laparoscopy, Postoperative nausea and vomiting.

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Introduction

Postoperative nausea and vomiting (PONV) are usually defined as any nausea, retching, or vomiting that occurs during the first 24 postoperative hours [1]. PONV is one of the most common causes of patient dissatisfaction after anesthesia, with a reported incidence as high as 63% after laparoscopic cholecystectomy [2]. PONV may delay patient discharge from the postanesthesia care unit (PACU) and increase unanticipated hospital admissions in outpatients. Therefore, prevention of PONV will

improve patient satisfaction and decrease overall health care costs.

Dexmedetomidine is a potent α_2-adrenergic agonist with potential applications in clinical anesthesia because of its broad-spectrum effects, which include anxiolytic, sedative, analgesic, anesthetic-sparing, sympatholytic, and hemodynamic-stabilizing properties [3]. The intra-operative use of dexmedetomidine as an anesthetic adjuvant has led to significant reductions in the use of opioids and inhalation anesthetics, reduction in the incidence of emergence agitation, a favorable recovery profile, and reduction of postoperative pain without adverse hemodynamic effects, and hence it may decrease PONV [3].

A pre-induction single dose of dexmedetomidine of 0.6–2 μg/kg resulted in the reduction of both inhalational anesthetic and opioid analgesic requirements during the intra-operative period [4,5]. We chose the 1 μg/kg dose to avoid the hypotension and bradycardia that occurred with 2 μg/kg [5]. The aim of the study was to compare the effect of a single dose of 1 μg/kg of dexmedetomidine to a single dose of 8 mg dexamethasone, after induction of anesthesia, on the incidence of PONV in patients undergoing laparoscopic cholecystectomy. Assessment of postoperative pain and calculations of total analgesic and antiemetic requirements during the first 24 h postoperatively were also recorded.

Materials and Methods

This was a randomized, controlled, double-blind study conducted with the approval of the Institutional Review Board and after receiving written informed consent from each participant. Over a period of 10 months, 86 adult patients scheduled for elective laparoscopic cholecystectomy agreed to participate in the study. Inclusion criteria included adult patients with American Society of Anesthesiologists (ASA) physical status I–II undergoing laparoscopic cholecystectomy for chronic calcular cholecystitis. Exclusion criteria included allergy to study medications, receiving antiemetic medication during the last 48 h before surgery, and body mass index above 35 kg/m^2. Patients were randomly allocated to receive an intravenous (IV) single dose of either 1 μg/kg of dexmedetomidine (Dexmed group, N = 43) or 8 mg dexamethasone (Dexa group, N = 43) after induction of anesthesia and just before skin incision. Randomization was based on computer-generated codes maintained in sequentially numbered opaque envelopes. We did not include a placebo control group because this would be unethical, as the patients were at risk of developing PONV according to Apfel's risk score [6].

Anesthesia management was performed similarly for both groups using a standard protocol. Patients were pre-medicated with IV midazolam (1–3 mg) in the preoperative holding area. Prophylactic antibiotic in the form of 1 g cefazolin sodium IV was given 30 min before induction. Patients were then transferred to the operating room (OR). Standard physiologic monitoring included electrocardiograph leads II & V, heart rate, arterial oxygen saturation (SpO_2) measured by pulse oximeter, non-invasive blood pressure, and end-tidal CO_2 ($ETCO_2$). After pre-oxygenation, anesthesia was induced with IV fentanyl 1 μg/kg and propofol 2–2.5 mg/kg, followed by IV rocuronium bromide 0.6 mg/kg to facilitate endotracheal intubation. The lungs were ventilated with a fraction of inspired oxygen (FIO_2) of 0.5 using a mixture of oxygen and air with volume-controlled ventilation. Patients were ventilated with a tidal volume (V_T) of 6–8 ml/kg, respiratory rate (RR) of 10–12 breaths/min, and inspiratory-to-expiratory ratio of 1 : 2. Ventilatory parameters (V_T, RR) were adjusted to maintain $ETCO_2$ tension around 35 mmHg. A forced-air warming system was used to maintain temperature above 36.0°C using a Bair-Hugger warmer (Arizant Medical, Eden Prairie, MN, USA).

Anesthesia was maintained with 1.0–2.5% end-tidal concentration sevoflurane in 50% oxygen and 50% air. Rocuronium boluses were given to maintain 1⁄4 to 2⁄4 twitches of train-of-four (Dräger, Trident NMT monitor, Telford, PA, USA). Fentanyl boluses and sevoflurane concentrations were adjusted to maintain the depth of anesthesia between 40 and 60 by using COVIDIEN BIS LoC 2 Channel (Dräger Medical GmbH, Lübeck, Germany). An orogastric tube was inserted orally (through another endotracheal tube inserted esophageally using Glidescope) after induction of anesthesia to deflate the stomach and was suctioned and removed just before extubation. During anesthesia, all patients received IV lactated Ringer's solution at a rate of 10 ml/kg. They were maintained on 2 ml/kg/h during recovery until they were able to tolerate oral fluids. The study drug was diluted to a total of 100 ml 0.9% sodium chloride and infused over a 15 min period. For dexmedetomidine, 2 ml of the drug (Precedex®, Hospira Inc., Lake Forest, IL, USA) was withdrawn and added to 98 ml of 0.9% sodium chloride injection to a total of 100 ml. After mixing well, the final concentration was 2 μg/ml. The doses were calculated and prepared by anesthesiologists who were not involved in the study. Data were collected by anesthesiologists who were blinded to the study drug.

All patients were put in a standard reverse Trendelenburg position (rT) during surgery with head up 30° and left lateral tilt 15° (the right side of the OR table was elevated 15°). Pneumoperitoneum was established with CO_2, and the intra-abdominal pressure was maintained at 12 mmHg. Laparoscopic cholecystectomy was performed under video guidance with four punctures of the abdomen. After gas deflation, all patients received 1 g paracetamol infusion over 15 min. In addition, 10 ml of 0.5% bupivacaine were injected locally at the four punctures of the abdomen for postoperative pain. Upon completion of surgery, atropine and neostigmine (1/2.5 mg) were given slowly IV to

restart spontaneous breathing, which was followed by tracheal extubation. Patients were sent to the recovery room and later to the ward.

During the preoperative visit, all patients were familiarized with a visual analogue scale (VAS) of 0–100 mm for PONV [7]. On this scale, a score of 0 meant no nausea, while a score of 100 meant the worst imaginable nausea. Occurrence of vomiting or retching was scored as 100. Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit, while retching was defined as making an effort to vomit without expulsion of gastric contents, and vomiting was defined as the forceful expulsion of even a small amount of upper gastrointestinal contents through the mouth [8]. During the first 24 h postoperatively, the total number of patients who had nausea and/or vomiting was calculated. If patients experienced nausea ≥ 60 on a 100 mm VAS, and/or retching or vomiting, or requested an antiemetic, a rescue antiemetic consisting of ondansetron 4 mg was given slowly intravenously. At 24 h postoperatively, patients were asked to rate their nausea throughout the study period on a 100 mm VAS.

Also, pain severity was assessed using a 100 mm VAS, on which 0 indicated no pain and 100 indicated the worst pain imaginable. As postoperative pain after laparoscopic cholecystectomy has been reported to be more intense during the first 4 h [9], we measured the pain score at the following intervals: on arrival in the PACU (T0) and hourly for the next 10 h (T1-T10). The Ramsay Sedation Score was used to assess sedation hourly during the 6 h after arrival in the PACU [10]. During the 24 h after surgery, tramadol 50–100 mg was given IV if the pain score was ≥ 40 mm on a 100 mm VAS. The total amounts of tramadol and ondansetron given during the 24 h after surgery were calculated for both study groups. Mean arterial blood pressure and heart rate were recorded at the following time points: T_0: just before giving study medication; T_1: 5 min after study medication; T_2: 30 min after study medication; T_3: 5 min after extubation; T_4: on arrival at the PACU; and then hourly for the next 6 h ($T_{5\text{-}10}$).

Data management

Study variables and data were coded and entered into a spreadsheet using the Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA). Descriptive data analysis was performed, and outcomes were compared between the two study groups and presented in the form of mean and standard deviation or number and percent. Chi-square and Student's t-test were used to assess significant differences in categorical and continuous variables, respectively.

Sample size was calculated based on the hypothesis that dexmedetomidine would detect a minimal difference of 50% and dexamethasone would detect a difference of 22%. The marginal error was set at $P < 0.05$, and the power of the study at 80%. Sample size (n) was calculated according to the following equation [11].

$$n = \frac{(z_{\alpha/2} + z_{\beta})^2 [r\theta_1(1 - \theta_1) + \theta_2(1 - \theta_2)]}{(\theta_1 - \theta_2)^2} = 43$$

Where α = the probability of type I error (significance level) (the probability of rejecting a true null hypothesis) = 0.05, β = the probability of type II error = the probability of failing to reject a false null hypothesis = (1 — 0.8) = 0.2, θ_1 = the true mean response rate of dexmedetomidine = 50% = 0.5, θ_2 = the true mean response rate of the control, dexamethasone = 22% = 0.22

The value of r = allocation ratio for Dexmed (n_1) to Dexa (n_2) groups = 1, z =1.96

$\theta_1 - \theta_2$ = the difference between the true mean response rates of group 1 (test drug [θ_1]) and group 2 (control [θ_2]).

Results

Table 1 shows the baseline characteristics for both study groups. There was no statistically significant difference between the two groups in age, gender, weight, ASA status, smoking, history of motion sickness, history of previous PONV, and duration of

Table 1. Characteristics of the Study Population

Variable	Dexmed group (N = 43)	Dexa group (N = 43)	P value
Continuous			
Age (yr)	31.1 ± 2.4	32.3 ± 2.1	0.7
Weight (kg)	69.4 ± 2.2	71.5 ± 3.1	0.8
Duration of anesthesia (min)	93.5 ± 15.3	95.9 ± 10.6	0.8
Duration of surgery (min)	75.7 ± 13.9	72.8 ± 16.4	0.9
Categorical			
Gender			
M	9 (21%)	6 (14%)	0.4
F	34 (79%)	37 (86%)	
ASA status			
I	33 (77%)	34 (79%)	0.7
II	10 (23%)	9 (21%)	
Smokers			
Yes	7 (16%)	5 (12%)	0.5
No	36 (84%)	38 (88%)	
History of motion sickness			
Yes	6 (14%)	3 (7%)	0.3
No	37 (86%)	40 (97%)	
History of previous PONV			
Yes	3 (7%)	4 (9%)	0.6
No	40 (93%)	39 (91%)	

Values are mean ± SD or number of patient (percentage). No significant differences ($P > 0.05$) between the two groups in age, gender, weight, ASA status, smoking, history of motion sickness, history of previous postoperative nausea and/or vomiting (PONV), and duration of surgery or duration of anesthesia.

Table 2. Number of Patients Who Experienced PONV within 24-h Postoperatively

Variable	Dexmed group (N = 43)	Dexa group (N = 43)	RR	95% CI	P value
Nausea					
Yes	5 (11.6%)	7 (16.3%)	0.7	0.24–2.05	0.5
No	38 (88.4%)	36 (83.7%)			
Retching					
Yes	2 (4.7%)	2 (4.7%)	1	0.14–6.77	1.0
No	41 (95.3%)	41 (95.3%)			
Vomiting					
Yes	2 (4.7%)	3 (7.0%)	0.66	0.11–3.89	0.6
No	41 (95.3%)	40 (93%)			
Overall PONV					
Yes	9 (20.9%)	12 (27.9%)	0.7	0.35–1.59	0.4
No	34 (79%)	31 (72%)			

Values are number of patient (percentage). RR: Relative risk, CI: Confidence interval. No significant differences (P > 0.05) between study groups regarding postoperative nausea, retching, vomiting or overall postoperative nausea and/or vomiting (PONV).

Table 3. Comparison of Severity of PONV and Intraoperative & Postoperative Medications

Variable (Mean ± SD)	Dexmed group (N = 43)	Dexa group (N = 43)	Mean of difference	95% CI	P value
Severity of PONV (VAS)	55 ± 29	65 ± 22	−10	−21.04 to 1.04	0.07
Ondansetron dose during 24 h (mg)	0.93 ± 0.15	1.03 ± 0.33	−0.1000	−0.2099 to 0.0099	0.07
Tramadol dose during 24 h (mg)	85 ± 5	110 ± 12	−25	−28.94 to −21.06	< 0.0001
Intra-operative fentanyl (μg)	95 ± 11	115 ± 18	−20	−26.40 to −13.60	< 0.0001
First analgesic request (min)	97 ± 31	83 ± 21	14	2.64 to 25.36	0.0163

Values are mean ± SD. CI: Confidence interval. No significant differences (P > 0.05) between study groups in the severity of postoperative nausea and/or vomiting (PONV) or ondansetron consumption during the first 24 h. There were significant differences (P < 0.05) between study groups regarding the mean total amount of intra-operative fentanyl and postoperative tramadol consumption. The first analgesic request was significantly delayed in the Dexmed group compared to the Dexa group (P = 0.02).

surgery or anesthesia. The incidence of PONV was 20.9% (9 patients) in the dexmedetomidine group compared to 27.9% (12 patients) in the dexamethasone group (P = 0.4) (Table 2). Also, Table 2 shows that neither nausea nor vomiting or retching was significant. The severity of PONV assessed by VAS was less in the Dexmed group compared to the Dexa group, but it did not reach statistical significance (P = 0.07) (Table 3). Also, fewer patients in the Dexmed group required an antiemetic compared to the Dexa group (16.3 vs. 23.3%; respectively), but the difference did not reach statistical significance (P = 0.5). The mean total amount of intra-operative fentanyl was significantly lower in the Dexmed group (P < 0.0001) (Table 3). Within the first 24 h postoperatively, the mean total amount of tramadol consumption was significantly lower in the Dexmed group (P < 0.0001) (Table 3). However, there was no significant difference in the mean total amount of ondansetron between the two groups (Table 3). When the VAS was used to assess pain, the severity of pain was significantly lower in the Dexmed group during the 4 h assessment after arrival in the PACU compared to the Dexa group (Fig. 1). The first analgesic request was significantly delayed in the Dexmed

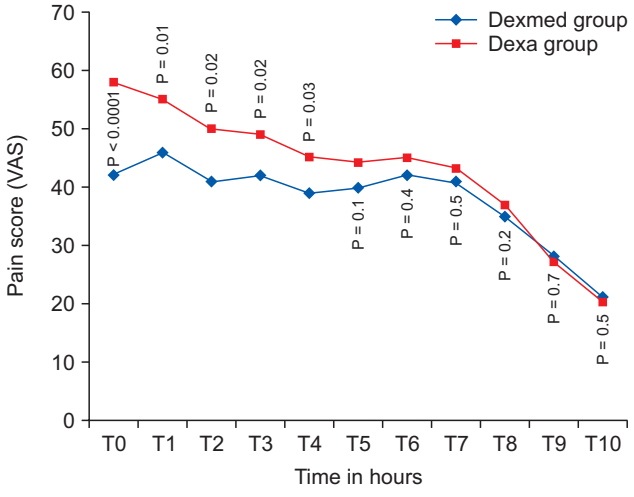

Fig. 1. Comparison of postoperative visual analogue scale (VAS) of pain between both groups. T0: on arrival at post-anesthesia care unit (PACU), (T1–T10): hourly for the next 10 h. The severity of pain was significantly lower (P < 0.05) in the Dexmed group on arrival at PACU and during the first 4-h assessment after arrival at the PACU compared to the Dexa group. No significant changes occurred after that (P > 0.05).

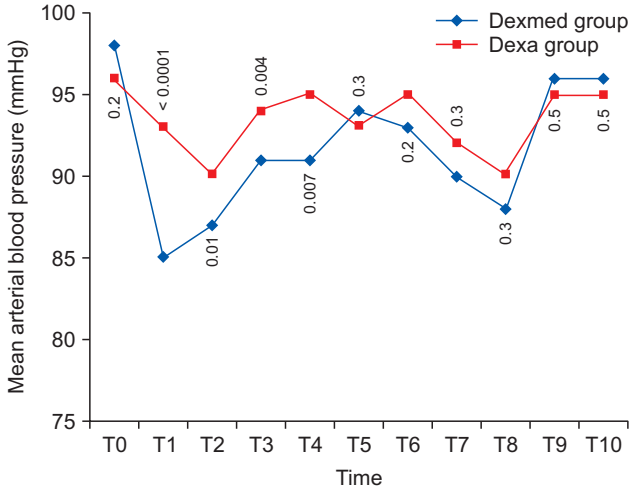

Fig. 2. Perioperative changes in mean arterial blood pressure in both groups. T0: just before giving study medication; T1: 5 min after study medication; T2: 30 min after study medication; T3: 5 min after extubation; T4: on arrival at the PACU; and then hourly for the next 6 h (T5–10). The mean arterial blood pressure was significantly lower ($P < 0.05$) in the Dexmed group after administration of dexmedetomidine till arrival at post-anesthesia care unit, but no significant changes occurred after that ($P > 0.05$).

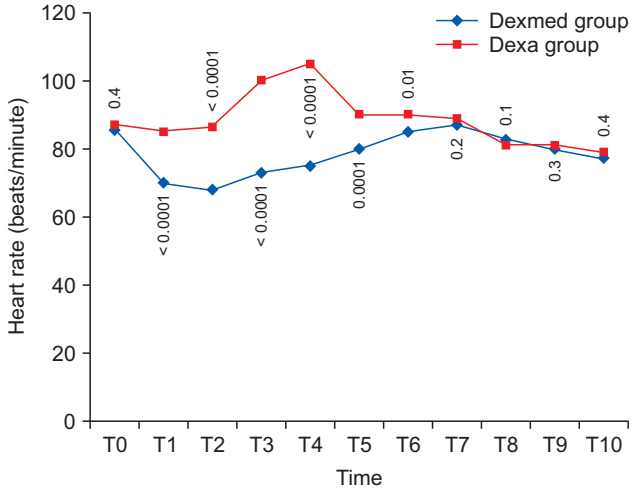

Fig. 3. Perioperative changes in heart rate in both groups. T0: just before giving study medication; T1: 5 min after study medication; T2: 30 min after study medication; T3: 5 min after extubation; T4: on arrival at post-anesthesia care unit (PACU); and then hourly for the next 6 h (T5–10). The heart rate was significantly lower ($P < 0.05$) in the Dexmed group after administration of dexmedetomidine till 2 h after arrival at PACU, but no significant changes occurred after that ($P > 0.05$).

group compared to the Dexa group ($P = 0.02$) (Table 3). During the 6 h after arrival in PACU, the mean Ramsey Sedation Score was significantly higher in the Dexmed group (4.2 ± 0.8) compared to the Dexa group (2.7 ± 0.9), with $P < 0.0001$. However, all patients in both groups were arousable and responded to oral commands in the PACU and in the ward.

The mean arterial blood pressure and heart rate were significantly lower in the Dexmed group after administration of dexmedetomidine and on arrival at the PACU, but no significant changes occurred after that (Figs. 2 and 3). However, after administration of study medication during anesthesia, ephedrine (10 mg) was required to treat hypotension in one patient in the Dexmed group compared with none in the dexamethasone group. Otherwise, the differences were not clinically significant. None of patients in either group were given atropine to treat bradycardia during anesthesia. In the post-anesthesia recovery unit, none of the patients needed ephedrine or atropine.

Discussion

The present study showed that dexmedetomidine reduces the incidence and severity of PONV similar to dexamethasone. During the first 24 h after laparoscopic cholecystectomy, it decreases early postoperative pain severity and reduces analgesic consumption. Our finding is consistent with Massad et al. [12], who found that dexmedetomidine reduced the incidence of PONV in female patients undergoing elective diagnostic laparoscopic gynecological procedures. They attributed their observation to the decrease in the overall consumption of anesthetic medications. In patients undergoing uvulo-palatopharyngoplasty, Abdelmageed et al. [13] reported that PONV was significantly reduced in the dexmedetomidine group during the first 24 h postoperatively. They attributed their finding to the reduction of postoperative morphine consumption in the dexmedetomidine group. Moreover, Goksu et al. [14] used dexmedetomidine for sedation during functional endoscopic sinus surgery under local anesthesia and reported a significantly lower incidence of PONV in the dexmedetomidine group, compared to a placebo group, without adverse effects. After giving a single dose of 0.5 μg/kg dexmedetomidine administered at the end of the surgery in female patients undergoing breast cancer surgery, Kim et al. [15] found that the overall incidence of PONV during the 24 h after surgery showed a trend toward a lower incidence in the dexmedetomidine group, but it did not reach statistical significance. However, they reported that dexmedetomidine significantly reduced the incidence of severe PONV during the first 24 h after surgery. Furthermore, they found that dexmedetomidine improved the quality of recovery (QoR-40), and reduced the rescue analgesic requirements during the first 24 h after surgery without prolonging recovery times or causing serious hemodynamic side effects. Their dose (0.5 μg/kg) may not have been sufficient to reach statistical significance in the prevention of PONV; that is why a dose of 1 μg/kg was used in our study. In their systematic review and meta-analysis, Blaudszun et al.

[16] concluded that perioperative systemic administration of α2-agonists decreases postoperative opioid consumption, pain severity, and nausea without delaying recovery times.

Possible explanations for the lower incidence of PONV in the dexmedetomidine group may be related to the reduced consumption of intra-operative and postoperative opioids and inhaled anesthetics [17]. Also, dexmedetomidine decreases noradrenergic activity as a result of binding to alpha-2 presynaptic inhibitory adreno-receptors in the locus coeruleus, which may result in an antiemetic effect [18]. Lastly, it may be related to the overall reduction in sympathetic outflow and catecholamine release caused by dexmedetomidine. High sympathetic tone and catecholamine release may trigger PONV [8].

The dexmedetomidine-induced opioid-sparing effect observed in the present study has also been documented by other investigators. Gurbet et al. [17] reported that patients who received dexmedetomidine required a lower cumulative amount of morphine during the first 48 h after total abdominal hysterectomy in spite of similar pain scores in the two studied groups. Also, Arain et al. [19] compared intra-operative dexmedetomidine to morphine sulfate in patients undergoing elective inpatient surgery and found that both groups had similar pain scores. However, the morphine group required 66% more morphine to achieve the same analgesic effect as the dexmedetomidine group. The reduction of postoperative pain by dexmedetomidine could be explained by the activation of the α_2-adrenoreceptor in the dorsal horn of the spinal cord, which inhibits the release of substance P, which modulates the transmission of nociceptive signals in the central nervous system, leading to reduction of nociceptive inputs during the acute postoperative period [20].

Contrary to our results, Lee et al. [21] reported that the incidence of PONV did not differ between a general anesthesia group who did not receive dexmedetomidine and a monitored anesthetic care group who received dexmedetomidine for closed reduction of nasal bone fracture. However, their dexmedetomidine group had their surgery under local anesthesia and was compared to a general anesthesia group. In addition, they assessed the PONV only in the PACU. The study by Shin et al. [22] found no significant difference between dexmedetomidine and control groups in the incidence of PONV, despite decreasing anesthetic consumption and maintenance of stable hemodynamics in the Dexmed group. However, the difference in the incidence of PONV between their study and our work may be related to the timing of dexmedetomidine dose (pre-anesthesia), type of surgery (gynecological), and sample size (only 21 patients in each group). Also, most importantly, they observed PONV only in the recovery room.

In the present study, we found that the incidence of PONV in the Dexa group was 27.9%. This finding is similar to previous reports [2,23,24] of use of dexamethasone as a prophylactic against PONV after laparoscopic cholecystectomy. The exact mechanism of the antiemetic action of dexamethasone is not well known. Elhakim et al. [25] suggested that dexamethasone might act as a serotonin receptor antagonist in the gastrointestinal tract. Others [26] proposed that dexamethasone might lead to a reduction in parasympathetic impulses to the brain by decreasing tissue inflammation around the surgery site.

Based on this study finding, dexmedetomidine has an effect similar to that of dexamethasone in reducing the incidence and severity of PONV. In addition, dexmedetomidine is superior to dexamethasone in reducing postoperative pain and total analgesic consumption during the first 24 h after laparoscopic cholecystectomy, without any major adverse effects. Further studies are needed to determine the optimum dose and timing of administration of dexmedetomidine to prevent PONV without effects on patient hemodynamics or sedation. We therefore conclude that a single dose of dexmedetomidine is appropriate for preventing PONV in patients undergoing laparoscopic cholecystectomy.

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