SCIENTIFIC ARTICLE

Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double-blinded study[☆]

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Abstract

Background and objectives: Intraoperative use of opioids may be associated with postoperative hyperalgesia and increased analgesic consumption. Side effects due to perioperative use of opioids, such as postoperative nausea and vomiting may delay discharge. We hypothesized that total intravenous anesthesia consisting of lidocaine and dexmedetomidine as an opioid substitute may be an alternative technique for laparoscopic cholecystectomy and would be associated with lower fentanyl requirements in the postoperative period and less incidence of postoperative nausea and vomiting.

Methods: 80 Anesthesiologists I–II adults were scheduled for elective laparoscopic cholecystectomy. Patients were randomly allocated into two groups to have either opioid-free anesthesia with dexmedetomidine, lidocaine, and propofol infusions (Group DL) or opioid-based anesthesia with remifentanil, and propofol infusions (Group RF). All patients received a standard multimodal analgesia regimen. A patient controlled analgesia device was set to deliver IV fentanyl for 6 h after surgery. The primary outcome variable was postoperative fentanyl consumption.

Results: Fentanyl consumption at postoperative 2nd hour was statistically significantly less in Group DL, compared with Group RF, which were $75 \pm 59\,\mu g$ and $120 \pm 94\,\mu g$ respectively, while it was comparable at postoperative 6th hour. During anesthesia, there were more hypotensive events in Group RF, while there were more hypertensive events in Group DL, which were both statistically significant. Despite higher recovery times, Group DL had significantly lower pain scores, rescue analgesic and ondansetron need.

Conclusion: Opioid-free anesthesia with dexmedetomidine, lidocaine and propofol infusions may be an alternative technique for laparoscopic cholecystectomy especially in patients with high risk for postoperative nausea and vomiting.

Anestesia venosa total livre de opioides, com infusões de propofol, dexmedetomidina e lidocaína para colecistectomia laparoscópica: estudo prospectivo, randomizado e duplo-cego

Resumo

Justificativa e objetivos: O uso de opioides no período intraoperatório pode estar associado à hiperalgesia e ao aumento do consumo de analgésicos no período pós-operatório. Efeitos colaterais como náusea e vômito no período pós-operatório, por causa do uso perioperatório de opioides, podem prolongar a alta. Nossa hipótese foi que a anestesia venosa total com o uso de lidocaína e dexmedetomidina em substituição a opioides pode ser uma técnica opcional para a colecistectomia laparoscópica e estaria associada a uma menor solicitação de fentanil e incidência de náusea e vômito no período pós-operatório.

Métodos: Foram programados para colecistectomia laparoscópica eletiva 80 pacientes adultos, estado físico ASA I-II. Os pacientes foram randomicamente alocados em dois grupos para receber anestesia livre de opioides com infusões intravenosas (IV) de dexmedetomidina, lidocaína e propofol (Grupo DL) ou anestesia baseada em opioides com infusões de remifentanil e propofol (Grupo RF). Todos os pacientes receberam um regime padrão de analgesia multimodal. Um dispositivo de analgesia controlada pelo paciente foi ajustado para liberar fentanil IV por seis horas após a cirurgia. O desfecho primário foi o consumo de fentanil no pós-operatório.

Resultados: O consumo de fentanil na segunda hora de pós-operatório foi significativamente menor no grupo DL do que no Grupo RF, 75 ± 59 µg e 120 ± 94 µg, respectivamente, mas foi comparável na sexta hora de pós-operatório. Durante a anestesia, houve mais eventos hipotensivos no Grupo RF e mais eventos hipertensivos no grupo DL, ambos estatisticamente significativos. Apesar de apresentar um tempo de recuperação mais prolongado, o Grupo DL apresentou escores de dor e consumo de analgésicos de resgate e de ondansetrona significativamente mais baixos.

Conclusão: A anestesia livre de opioides com infusões de dexmedetomidina, lidocaína e propofol pode ser uma técnica opcional para a colecistectomia laparoscópica, especialmente em pacientes com alto risco de náusea e vômito no pós-operatório.

Introduction

Opioids are widely used for perioperative analgesia. However, the intraoperative use of large bolus doses or continuous infusions of potent opioids may be associated with postoperative hyperalgesia and increased analgesic consumption.[1] When it comes to 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 postoperative pain after laparoscopic cholecystectomy (LC) is complex in nature and growing evidence suggests that its treatment should be multimodal and opioid sparing to accelerate recovery.[2,3] In spite of multimodal analgesic strategies, which consist of opioids, dexamethasone, non-steroidal anti-inflammatory drugs, and local anesthetics applied into the surgical wound, postoperative pain and PONV are still common complaints reported after LC. It has been suggested that esmolol infusion may be an acceptable alternative to remifentanil infusion for ambulatory laparoscopic surgery[4–6] and opioid-free anesthetic techniques with esmolol infusion is associated with reduced postoperative opioid consumption.[5,6]

Dexmedetomidine is a highly selective alfa-2 adrenoceptor agonist that provides sedation, analgesia, and sympatholysis. Although perioperative intravenous dexmedetomidine administration is associated with a reduction in postoperative pain intensity, analgesic consumption and nausea,[7–12] the analgesic property of dexmedetomidine is less effective compared with remifentanil.[13] Intravenous lidocaine has been described as having analgesic, anti-hyperalgesic, and anti-inflammatory properties. Intravenous lidocaine infusion in the perioperative period is safe and has clear advantages, such as decreased intraoperative anesthetic requirements, lower pain scores, reduced postoperative analgesic requirements, as well as faster

return of bowel function and decreased length of hospital stay.[14–20] Therefore, we hypothesize that total intravenous anesthesia (TIVA) consisting of lidocaine combined with dexmedetomidine as an opioid substitute is a feasible technique for LC and would be associated with lower fentanyl requirements in the early postoperative period and less incidence of PONV.

The present prospective, randomized, double-blinded study was designed to compare the effect of opioid-free (using dexmedetomidine, lidocaine and propofol infusions) and opioid-based (using remifentanil and propofol infusions) TIVA techniques on postoperative pain intensity and the incidence of side effects in patients scheduled for LC.

Methods

After obtaining the Ethics Committee's approval and the patients' written informed consent, the study was conducted between June 2012 and April 2013 at our university hospital. Patients scheduled for elective laparoscopic cholecystectomy, who had the American Society of Anesthesiologists (ASA) I or II physical status, and were 20–60 years of age were included in this study. The exclusion criteria were: a body mass index >35 kg m^{-2}, pregnant, breast-feeding or menstruating women, hepatic, renal or cardiac insufficiency, diabetes, history of chronic pain, alcohol or drug abuse, psychiatric disease, allergy or contraindication to any of the study drugs, inability to comprehend pain assessment and to use a patient-controlled analgesia

(PCA) device. Written informed consent was obtained from patients before randomization.

Randomization and blinding

Patients were randomly allocated into two groups to have either opioid-free anesthesia (Group DL) with dexmedetomidine (0.6 μg kg^{-1} loading, 0.3 μg kg^{-1} h^{-1} infusion), lidocaine (1.5 mg kg^{-1} loading, 2 mg kg^{-1} h^{-1} infusion), and propofol infusions or opioid-based anesthesia (Group RF) with fentanyl, and remifentanil (0.25 μg kg^{-1} min^{-1}), and propofol infusions (Fig. 1).

Simple randomization was done using 80 opaque sealed envelopes, 40 for each group, indicating group assignment and describing the anesthetic protocol. Before anesthesia induction, an anesthesiologist opened the next envelope in the sequence to reveal the treatment allocation. This anesthesiologist only prepared the study medications and was not involved in preoperative and postoperative data collection or anesthesia management of the patients.

Time chart of anesthetic management is shown in Table 1. The drugs were delivered in 10 mL and 50 mL syringes labeled as ''loading'' or ''infusion'' respectively. To ensure proper blinding, the loading doses of drugs (dexmedetomidine and lidocaine in Group DL or fentanyl and normal saline in Group RF) were calculated according to the patient's body weight and diluted to a 10 mL volume labeled as ''loading-1'' and ''loading-2'' in order of administration. The infusion drugs (dexmedetomidine and lidocaine in Group DL or remifentanil and normal saline in Group RF) were
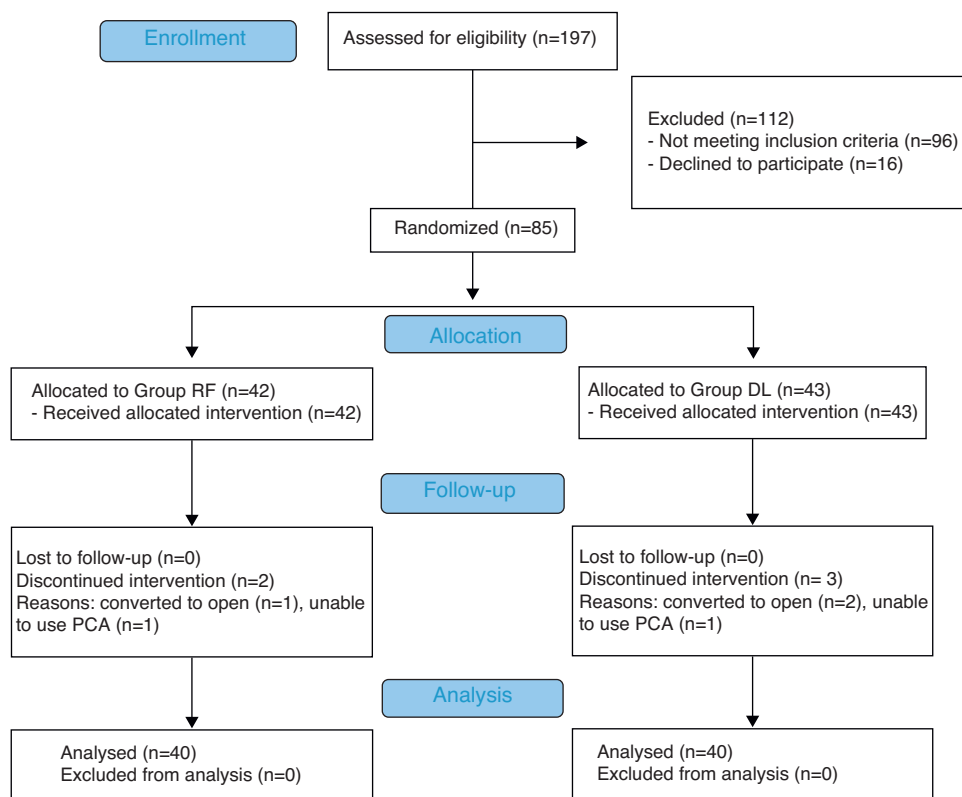

Figure 1 Flow of the participants through each stage of randomization.

Table 1 Time chart of anesthetic management.

Premedication	Loading (10 min)	Induction	Maintenance		
A↓			B↓	C↓	D↓
Group DL					
Midazolam (0.03 mg kg^{-1})	**Loading 1:** Dexmedetomidine (0.6 µg kg^{-1})	**Infusion 1:** Dexmedetomidine (0.3 µg kg^{-1} h^{-1}) (0.3 mL kg^{-1})			
		Loading 2: Lidocaine (1.5 mg kg^{-1}) Propofol (1.5 mg kg^{-1})	**Infusion 2:** Lidocaine (2 mg kg^{-1} h^{-1}) (0.1 mL kg^{-1}) Propofol (3–12 mg kg^{-1} h^{-1})		
Group RF					
Midazolam (0.03 mg kg^{-1})	**Loading 1:** Fentanyl (2 µg kg^{-1})	**Infusion 1:** Remifentanil (0.25 µg kg^{-1} min^{-1}) (0.3 mL kg^{-1})			
		Loading 2: 0.9% Saline Propofol (1.5 mg kg^{-1})	**Infusion 2:** 0.9% Saline infusion (0.1 mL kg^{-1}) Propofol (3–12 mg kg^{-1} h^{-1})		

A, Baseline hemodynamic values recorded; B, Endotracheal intubation; C, 'Infusion 2' was stopped after gallbladder extraction; D, End of surgery, propofol infusion and 'Infusion 1' was stopped.

prepared in 50 mL syringes and labeled as ''infusion-1'' and ''infusion-2'' respectively.

Anesthetic technique

At the preoperative holding area, patients were instructed on the use of the numerical rating scale (NRS) and patient controlled analgesia (PCA) pump. An anesthesiologist who is blinded to the study groups performed all procedures. On arrival at the operating room, standard monitoring was applied consisting of ECG, non-invasive blood pressure, pulse oximetry, temperature, and bispectral index (BIS). After premedication with intravenous midazolam 0.03 mg kg^{-1}, baseline heart rate and mean arterial blood pressure (MAP) were determined which is the average of three consecutive measurements. Intravenous balanced crystalloid solution (Isolyte-S) was started and pre-oxygenation with 5 L min^{-1} of pure oxygen was performed during administration of loading doses. Before induction, patients in Group DL received 0.6 µg kg^{-1} dexmedetomidine (loading-1) diluted to a total volume of 10 mL and infused in 10 min. To avoid bias, patients in Group RF received fentanyl 2 µg kg^{-1} in the same fashion. At the induction, dexmedetomidine or remifentanil infusions (in 1 µg mL^{-1} and 50 µg mL^{-1} concentrations respectively, labeled as infusion-1) at 0.3 mL kg^{-1} h^{-1} were started. Lidocaine at 1.5 mg kg^{-1} (loading-2) in Group DL or normal saline in Group RF and propofol at 1.5 mg kg^{-1} was administered. Lidocaine (20 mg/mL) or normal saline infusions (infusion-2) at 0.1 mL kg^{-1} h^{-1} and propofol infusion at 10 mg kg^{-1} h^{-1} was started immediately after loading doses. Vecuronium at 0.1 mg kg^{-1} IV was given to facilitate tracheal intubation.

The dose of dexmedetomidine was based on a literature[21] that compared dexmedetomidine-based versus fentanyl-based TIVA and found no difference in extubation and discharge times. The dose of remifentanil was based on studies, achieving sufficient analgesia for LC.[22,23]

Dexmedetomidine and lidocaine infusions in Group DL or remifentanil and normal saline infusions in Group RF keep constant during surgery. Propofol infusion rate was adjusted to 3–12 mg kg^{-1} h^{-1} to maintain the mean arterial pressure (MAP) within ±20% of the baseline value, and to maintain a BIS reading below 50. The lidocaine or normal saline administration was terminated after gallbladder extraction or aproximately10 min before the end of surgery. Skin incisions were infiltrated with 15–20 mL of bupivacaine 0.5% including 1/80.000 adrenaline before closure. Dexmedetomidine or remifentanil and propofol infusions were terminated during skin closure. Residual neuromuscular blockade was antagonized with neostigmine 0.05 mg kg^{-1} and atropine 0.02 mg kg^{-1} and tracheal extubation was performed when patients achieved a regular spontaneous breathing pattern.

The lungs were mechanically ventilated with a mixture of oxygen in air (FiO$_2$: 50%, tidal volume 7–10 mL kg^{-1}, respiratory rate 10–14 min^{-1}) to obtain an end-tidal carbon dioxide (EtCO$_2$) value between 30 and 35 mm Hg. Supplemental neuromuscular blockade was achieved with vecuronium after assessment of neuromuscular function with train-of-four. Intraoperative normothermia was maintained with forced air warming blankets positioned over the exposed parts of the body and IV crystalloid was administered at a rate of 6–12 mL kg^{-1} h^{-1} during anesthesia. All patients wore anti-embolic stockings and received enoxaparin 40 mg subcutaneously before surgery; dexamethasone 8 mg and dexketoprophen trometamol 50 mg IV after anesthesia induction; and paracetamol 1 g IV after gallbladder extraction.

Non-invasive blood pressure was assessed at least at 3 min of interval during anesthesia. Hypotension (MAP < 60 mm Hg) was treated with ephedrine 10 mg IV and bradycardia (heart rate < 45 bpm) was treated with atropine 0.5–1 mg IV. A bolus

IV dose of 0.1 mg nitroglycerine was administered when MAP > 120 mmHg.

Surgery

Surgeons who were experienced in laparoscopic cholecystectomy performed the operations using standard 4-trocar technique. After endotracheal intubation a nasogastric tube was inserted and stomach content was aspirated. A blunt-tipped 12-mm trocar was used to access the peritoneal cavity. Pneumoperitoneum was achieved with carbon dioxide, and intra-abdominal pressure was maintained at 12–14 mm Hg throughout surgery. Three additional 5-mm ports were introduced and patients were positioned in 30 degrees anti-Trendelenburg position and rotated toward the left side to facilitate exposure of the gallbladder. At the end of surgery, patients were returned to supine position and the inflated carbon dioxide was carefully evacuated by manual compression of the abdomen.

Postoperative care

A PCA pump was ready to use immediately after extubation for 6 h. The PCA pump was set to deliver fentanyl IV with a bolus dose of 20 μg, a lockout of 5 min, without continuous infusion and dose limit. Transition from PACU to surgical ward was considered to be safe when the patient had achieved a Modified Aldrete Score $\geq$9. Although LC is established as a day-case procedure, our protocol was designed to admit all patients for 24 h to ensure adequate follow-up of patients and for proper data collection. Patients were allowed to drink water 4 h after extubation. Postoperative nausea and vomiting was treated with metoclopramide 10 mg IV (with 8 h of time interval) and if not effective in 15 min ondansetron 4 mg IV was administered. After PCA was stopped all patients received oral doses of paracetamol 500 mg (4 × 1) and dexketoprophen trometamol 25 mg (3 × 1) and tramadol 100 mg as a rescue analgesic. Investigators blinded to treatment allocation and with no access to the intraoperative records performed all outcome assessments in the post-anesthesia care unit (PACU) and surgical ward. Pain scores were assessed using the 11-point NRS (0 corresponding to no pain and 10 to the worst imaginable pain).

The following data were collected: demographic characteristics of the patients studied, history of smoking, motion sickness and PONV, duration of surgery and anesthesia, amount of drugs used during surgery, amount of fentanyl used in postoperative period for 6 h, NRS, incidence of PONV and other adverse events.

Statistical analysis

The primary outcome variable was fentanyl consumption used for pain relief in the first 6 h after extubation. Secondary outcome measures were recovery times, the incidence of PONV, and maximal overall NRS pain score (max-NRS) at the surgical ward after PCA was discontinued. The sample size requirement was based on preliminary data from a previous pilot study with ten patients in which fentanyl requirements were 200 ± 152 μg in Group RF and 120 ± 88 μg in Group DL. Thus, at an alpha risk of 0.05, 39 patients per group would provide 80% power and detect a 40% reduction in fentanyl consumption in a treatment group. The results are presented as medians and quartiles. Descriptive variables are given as percentages. The Mann–Whitney U test was used to compare the continuous parameters. Fisher's exact test was used to compare non-parametric variables. All statistical analyses were performed using the commercially available SPSS v.16.0 software package (SPSS Inc., Chicago, IL, USA). A probability value of less than 0.05 was considered statistically significant.

Results

Of the 197 patient approached, 66 did not meet the criteria for inclusion, 14 refused to participate in the study, 4 turned to open surgery, leaving 80 patients suitable to be enrolled in this investigation (Fig. 1).

The patients' characteristics and perioperative data are detailed in Table 2. Patient characteristics were not significantly different among groups. Propofol consumption, orientation and PACU discharge times were significantly higher in Group DL.

Baseline values of heart rate and mean arterial pressure were comparable between the groups. Heart rate and mean arterial pressure values after induction, at intubation and 1st, 4th, 7th and 10th min of pneumoperitoneum were significantly higher in Group DL (Fig. 2). There were more patients requiring ephedrine to treat hypotension in Group RF, and more patients requiring nitroglycerine to treat hypertension in Group DL. Nitroglycerine use in Group DL ($n = 11$) was mostly at the beginning of the pneumoperitoneum ($n = 9$). Other side effects were comparable among groups, except ondansetron use (Table 3). None of the patients in Group DL require ondansetron to treat PONV ($p < 0.05$). None of the patients in both groups reported recall of intraoperative events and complained about any side effects that may be related to lidocaine (cardiac arrhythmia, perioral numbness, metal taste, tinnitus and visual disturbances).

Three patients in Group RF and 6 patients in Group DL with minimal pain preferred not to use PCA ($0 > 0.05$). Postoperative fentanyl consumption 2 h after extubation and max-NRS and rescue analgesic need after cessation of fentanyl PCA was significantly lower in Group DL (Table 4). Cumulative postoperative fentanyl consumption 4 and 6 h after extubation were comparable among groups (Fig. 3).

Discussion

The results of this study indicate that opioid-free TIVA with dexmedetomidine, lidocaine and propofol infusions when compared with opioid-based TIVA with remifentanil and propofol infusions, is associated with lower fentanyl requirements in the early postoperative period (0–2 h) after LC. Prolonged analgesic effect of dexmedetomidine may explain this finding, but total dexmedetomidine consumption in Group DL was <1 μg kg^{-1} in most cases and patients in Group RF had preoperative fentanyl administration which might have also prolonged analgesic effect. So, opioid-induced

Table 2 Demographic Characteristics and Perioperative Data.

	Group RF n = 40	Group DL n = 40	P
Male/female	13/27	12/28	NS
Age (yr)	43.8 ± 9.3	43.1 ± 10.6	NS
Weight (kg)	79.2 ± 14.4	74.2 ± 14.7	NS
Height (cm)	1.65 ± 0.08	1.65 ± 0.09	NS
Body mass index (kg m^{-1})	28.9 ± 4.1	27.2 ± 3.9	NS
ASA I/II	31/9	34/6	NS
History of smoking: n (%)	10 (25)	13 (33)	NS
History of previous PONV: n (%)	4 (10)	7 (18)	NS
History of motion sickness: n (%)	1 (2.5)	1 (2.5)	NS
Duration of surgery (min)	57.5 (45.2–68.8)	50.5 (41.2–68)	NS
Duration of anesthesia (min)	70 (57.8–79.5)	64.5 (51–81.2)	NS
Propofol doses for maintenance (mg kg^{-1} h^{-1})	5.18 ± 1.15	6.23 ± 1.47	0.003
Remifentanil consumption (μg)	1430 ± 592	–	–
Dexmedetomidine consumption (μg)	–	71 ± 19	–
Lidocaine consumption (mg)	–	256 ± 90	–
Extubation time (min)	9 (7–12.8)	10 (7–16)	NS
Orientation time (min)	13 (10–15.8)	14 (12–21)	0.045
PACU discharge time (min)	10 (10–15)	15 (10–20)	<0.001

Data are presented as relative number of patients, mean ± standard deviation, median (25th–75th percentile), or absolute number (percentage).
NS, not significant; ASA, American Society of Anesthesiologists; PONV, postoperative nausea and vomiting; PACU, post-anesthesia care unit.

hyperalgesia seems to be more reasonable for this finding. Cumulative fentanyl consumption becomes comparable at 4th and 6th hours postoperatively. This might be due to the treatment of postoperative pain with another potent opioid (fentanyl) that might cause hyperalgesia and/or tolerance. If we could make the postoperative pain treatment opioid-free, the analgesic consumption in Group DL might continue to be significantly lower at 4th and 6th h postoperatively. Thus, the max-NRS scores and rescue analgesic need after cessation of fentanyl PCA was significantly lower in Group DL.

Potent opioids are usually have to be used to control the intraoperative cardiovascular instability due to pneumoperitoneum in LC.[24] It has been reported that in patients undergoing LC, intraoperative infusion of lidocaine,

in combination with low doses of opioids was associated with reduced intraoperative and postoperative opioid requirements.[18,19] Park et al.[25] reported that pain scores after LC were reduced in the early postoperative period by the addition of dexmedetomidine in the multimodal analgesic regimen. Dexmedetomidine has mild analgesic properties than opioids have; it has been used as an opioid substitute in various surgical interventions[21,26–28] and is found to be associated with less postoperative pain[21,27] and PONV[21,27,28] but slow recovery.[26,27] Also, dexmedetomidine use (with some fentanyl support) as a remifentanil substitute in TIVA during gynecologic video-laparoscopic surgery was found to be effective.[29] But, laparoscopic cholecystectomy is unique compared with other laparoscopic procedures and
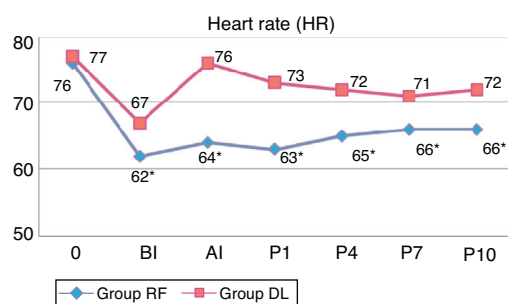

Figure 2 Changes in heart rate between groups during intra-operative periods. 0: baseline values, BI: before intubation (after induction), AI: after intubation, P1: 1st minute of pneumoperitoneum, P4: 4th minute of pneumoperitoneum, P7: 7th minute of pneumoperitoneum, P10: 10th minute of pneumoperitoneum. *: $p < 0.05$ between groups

Figure 3 Changes in mean arterial pressure between groups during intraoperative periods. 0: baseline values, BI: before intubation (after induction), AI: after intubation, P1: 1st minute of pneumoperitoneum, P4: 4th minute of pneumoperitoneum, P7: 7th minute of pneumoperitoneum, P10: 10th minute of pneumoperitoneum. *: $p < 0.05$ between groups
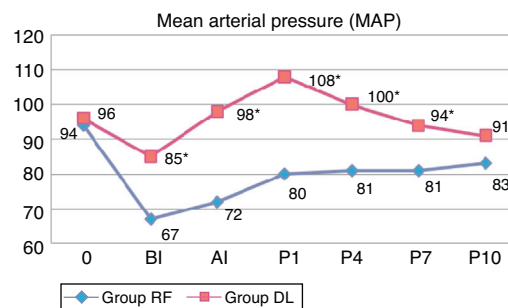
Table 3 Incidence of events and side effects.

	Group RF n = 40	Group DL n = 40	P value
Ephedrine use	8 (20)	1 (3)	0.029
Nitroglycerine use	0	11 (28)	< 0.001
Intraoperative bradycardia	4 (10)	0	NS
Intraoperative tachycardia	0	1 (3)	NS
Sub-hepatic drain use	6 (15)	5 (13)	NS
Shivering	10 (25)	3 (8)	NS
Nausea	13 (33)	5 (13)	NS
Vomiting	5 (13)	1 (3)	NS
Ondansetron use	6 (15)	0	0.026

Values are presented as number of patients (percentage).
NS, not significant.

associated with higher sympathoadrenal response, so we want to increase the analgesic effects of dexmedetomidine and lidocaine by combining these agents.

It has been demonstrated that dexmedetomidine enhances the local anesthetic action of lidocaine in pigs[30] and improves the quality of anesthesia and perioperative analgesia when added to lidocaine for IV regional anesthesia.[31] Dexmedetomidine use, combined with lidocaine and propofol was defined for tracheal intubation without the use of muscle relaxants and intubation conditions were found to be statistically more satisfactory compared with fentanyl.[32] But, the combined analgesic effect of dexmedetomidine and lidocaine in total intravenous general anesthesia was not evaluated before our study.

Previous studies in patients undergoing LC showed that intraoperative esmolol infusion instead of opioids is associated with reduced postoperative opioid requirements.[5,6] In a similar study with ours, Collard et al.[5] compared fentanyl, remifentanil and esmolol adjunct to desflurane anesthesia for LC and patients in esmolol group used 100 μg (median) fentanyl in the postoperative period (2 h), which seems comparable with our opioid-based group. In our study, we used propofol infusion instead of desflurane and that was found to be associated with less postoperative analgesic consumption during remifentanil-based anesthesia.[22,33] Also, propofol has anti-emetic properties. Propofol use instead

of inhalational anesthetics in LC seems more suitable in this opioid-free concept. But, it has been suggested that dexmedetomidine may delay recovery, as an adjuvant to propofol during TIVA.[34] This is consistent with our study, while the orientation and PACU discharge time was significantly higher in Group DL. This may be due to the higher infusion rate of propofol to control the hemodynamic response to pneumoperitoneum.

The double-blind fashion of the study may be a limitation; as the infusion rates of dexmedetomidine and remifentanil were constant, nitroglycerine or ephedrine had to be used to control the hemodynamic fluctuations in some patients. As 28% of patients in Group DL were hypertensive at the beginning of the pneumoperitoneum and regarding higher nitroglycerine use in Group DL, the protocol can be modified with addition of small amount of opioid or a higher infusion rate for dexmedetomidine (1 g kg^{-1} loading and 0.2–0.5 g kg^{-1} h^{-1} maintenance) which might be more appropriate. It may be reasonable to prefer delayed recovery to postoperative increased pain intensity and PONV for some patients. Also, desflurane use instead of propofol (maximum dose was limited to 12 mg kg^{-1} h^{-1}) in Group DL might alleviate hypertensive events and be associated with shorter recovery.

Postoperative pain after LC is highly variable among patients. There is need for individualized anesthesia technique and postoperative analgesic treatment. As

Table 4 Postoperative pain intensity analysis.

	Group RF n = 40	Group DL n = 40	p
Postoperative fentanyl consumption			
0–2 h (μg)	120 ± 94 (110)	75 ± 59 (60)	0.04
0–4 h (μg)	185 ± 143 (160)	123 ± 100 (120)	NS
0–6 h (μg)	235 ± 175 (220)	162 ± 142 (150)	NS
Max-NRS	4 (2–6)	3 (2–4)	0.028
Max-NRS-cough	5.5 (3–7)	4 (3–5)	0.015
Shoulder pain (n)	7 (18%)	10 (25%)	NS
Rescue analgesic need (n)	19 (48%)	9 (23%)	0.034

Data are presented as mean ± standard deviation (median), median (25th–75th percentile), or absolute number of patients (percentage).
NS, not significant, Max-NRS, maximal numeric rating scale score for pain intensity at the surgical ward after PCA was discontinued.

dexmedetomidine and lidocaine decreases the anesthetic and opioid consumption, it is reasonable to add these agents in an anesthesia regimen for LC. Former opioid addiction or high-risk for PONV may be reasons for preference of this opioid-free technique.

In conclusion: when compared with opioid-based TIVA with remifentanil and propofol infusions, opioid-free TIVA with dexmedetomidine, lidocaine and propofol infusions is associated with lower fentanyl requirements in the early postoperative period (0–2 h). Also, max-NRS, rescue analgesic need and ondansetron use was significantly lower in the opioid-free group in the first postoperative day. Despite prolonged recovery times, opioid-free anesthesia with dexmedetomidine, lidocaine and propofol may be an alternative technique for LC in selected patients especially with high risk of PONV.

Conflicts of interest

The authors declare no conflicts of interest.

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