KLİNİK ÇALIŞMA / CLINICAL RESEARCH

A COMPARISON OF THE EFFECTS OF INTRAOPERATIVE ESMOLOL AND LIDOCAINE INFUSIONS ON POSTOPERATIVE ANALGESIA

POSTOPERATİF AĞRI ÜZERİNE İNTRAOPERATİF İNFÜZYON ESMOLOL VE LİDOKAİN ETKİLERİNİN KARŞILAŞTIRILMASI

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SUMMARY

Objective: *In this study, we aimed to compare the effects of intraoperative esmolol, lidocaine and saline infusions on postoperative pain and opioid requirement in laparoscopic cholecystectomy.*

Method: *In this prospective randomized study 48 ASA physical status I-II patients were enrolled. Patients received an intravenous (IV) injection of 1 mg kg^{-1} esmolol (Group E), 1.5 mg kg^{-1} lidocaine (Group L) or 10 mcg remifentanyl (Group C) prior to the induction of anesthesia. Throughout surgery patients were infused with 50 mcg kg^{-1} min^{-1} esmolol (IV, Group E) or 2 mg kg^{-1} min^{-1} lidocaine (IV, Group L) or 10mL h^{-1} saline (Group C). Visual analog scale (VAS) in the postoperative 24 hours total fentanyl consumption and adverse drug events were recorded.*

Results: *Fentanyl consumption in the post-anesthesia care unit (PACU) was 50±11 mcg for Group E, 75±18 mcg for Group L and 100± 27 mcg for Group C ($p< 0.05$). In the postoperative 24 hours patients in Group E consumed significantly less fentanyl than those in Group L and C ($p=0.000$).*

Conclusion: *Esmolol infusion decreased opioid consumption during the 24-h postoperative period more effectively than lidocaine infusion and saline. Also esmolol might be a useful adjuvant for early recovery of bowel functions.*

KEY WORDS: *Esmolol; lidocaine; postoperative pain ; opioid requirement;*

ÖZET

Amaç: *Bu çalışmada laparaskopik kolesistektomi yapılan hastalarda intraoperatif esmolol, lidokain ve salin infuzyonunun postoperatif ağrı ve opioid gereksinimi üzerine etkilerini karşılaştırmayı amaçladık.*

Yöntem: *Bu prospektif randomize çalışmaya ASA I-II olan 48 hasta dahil edildi. Hastalara anestezi indüksiyonu öncesi 1 mg kg^{-1} esmolol (Grub E), 1.5 mg kg^{-1} lidokain (Grup L) veya 10 mcg remifentanil (Grup C) intravenöz (IV) enjeksiyonu uygulandı. Aynı zamanda, ameliyat boyunca hastalara 50 mcg kg^{-1} dk^{-1} esmolol (IV, E Grubu) veya 2 mg kg^{-1} dk^{-1} lidokain (IV, Grup L) veya 10 mL $saat^{-1}$ serum fizyolojik (C Grubu) infüzyonu verildi. Tüm hastaların görsel analog skalası (VAS), 24.saatte hastaların gaz çıkarma zamanları, toplam fentanil tüketim miktarı ve ilaç yan etkileri kaydedildi.*

Bulgular: *Anestezi sonrası bakım ünitesinde (PACU) fentanil tüketimi Grup E için 50±11 mcg, Grup L için 75±18 mcg, Grup C için 100± 27 mcg idi ($p< 0.05$). Cerrahi sonrası 24 saat içinde fentanil tüketimi Grup E'de, Grup L ve C'e göre önemli oranda düşük saptandı ($p=0.000$).*

Sonuç: *Esmolol infüzyonu, lidokain ve salin infüzyonuna göre postoperatif 24 saatlik dönemdeki fentanil ihtiyacını belirgin olarak azaltmaktadır. Aynı zamanda, esmolol postoperatif barsak fonksiyonlarının erken düzelmesinde yararlı olabilir.*

ANAHTAR KELİMELER: *Esmolol; lidokain; postoperatif ağrı; opiod gereksinimi;*

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INTRODUCTION

Laparoscopic cholecystectomy is a common outpatient procedure. Obtaining optimal postoperative analgesia, preventing nausea and vomiting, maintaining hemodynamic stability and normalization of intestinal motility are the primary concerns for this ambulatory surgery. In contrast to other laparoscopic procedures, pain management following laparoscopic cholecystectomies represents a particular challenge due to the mixed nature of pain, which includes visceral pain, incisional pain and shoulder pain (1-2) . Although multimodal analgesia is common in laparoscopic cholecystectomies, postoperative opioid administration is frequently necessary (3). Postoperative opioid use can cause sedation, respiratory depression, emesis, vomiting and ileus, thereby delaying recovery times (4).

Lidocaine is used as an adjuvant in multimodal analgesia techniques because of its anti-inflammatory effects and its effects on neural responses to pain. Systemic lidocaine can depress spike activity, amplitude and conduction time in both myelinated A-delta and unmyelinated C fibers. Although lidocaine is a safe agent, its dose-related side effects in the CNS limit its usage in anesthesia (5-6).

In the literature, intraoperative infusions of esmolol, a cardio-selective β_1 adrenergic receptor antagonist, have been used as an adjuvant to decrease perioperative opioid consumption and facilitate fast-tracking recovery (7-8). The purpose of this prospective randomized study is to compare the effects of intraoperative lidocaine (2 mg kg^{-1} h^{-1}), esmolol (50 mg kg^{-1} h^{-1}) and saline infusions on intraoperative anesthetic agent consumption, postoperative opioid use and the number of patients exhibiting flatus by 24 h following laparoscopic cholecystectomy.

METHODS

Approval for this study (Ethical Committee No: 34) was provided by the Ethical Committee of the Ministry of Health Diskapi Yildirim Beyazit Training and Research Hospital in Ankara, Turkey. Sixty patients between the ages of 20 and 70 with ASA I or II classification statuses who had provided written informed consent were included in the study. The exclusion criteria included the following: an ASA physical status of III or greater, diabetes, BMI > 40, chronic use of beta-adrenergic receptor antagonists or a history of hepatic, renal or cardiac disease. Of the original 60 patients, 9 did not meet the inclusion criteria and 3 refused to participate and were thus excluded (Figure 1). The remaining 48 patients were randomly allocated to one of three groups (Group E (n = 16) esmolol, Group L (n = 16) lidocaine, Group C (n=16) control) using a computer-generated random table.

Patients were premedicated with an intramuscular (IM) injection of midazolam (0.05 mg kg^{-1}) 30 min prior to surgery. Routine monitoring of all patients was conducted using ECG, pulse oximetry and non-invasive blood pressure measurements. After IV administration of 1 mg kg^{-1} esmolol (Group E), 1.5 mg kg^{-1} lidocaine (Group L) or remifentanil 10 mcg IV (Group C), anesthesia was induced with 2 mg kg^{-1} propofol and 0.5 mg kg^{-1} rocuronium (IV). Following muscular relaxation, tracheal intubation was performed, and $ETCO_2$ was maintained between 32-42 mmHg with a fresh gas flow rate of 4 L min^{-1}. Anesthesia was maintained with 50% nitrous oxide in oxygen and sevoflurane to maintain blood pressure and heart rate within 20% of baseline values. End-tidal sevoflurane concentrations were continuously measured during the breathing cycle using a precalibrated gas monitor (Scio Four Oxi plus Medibus Fabius GS; Drager Medical, Lubeck, Germany).

Signs of inadequate anesthesia included an increase in heart rate (HR), a mean arterial pressure (MAP) of more than 20% from baseline and autonomic signs, such as mydriasis or lacrimation. When inadequate anesthesia was observed, the sevoflurane concentration was increased and, if necessary, 0.5 mcg kg^{-1} fentanyl was administered IV.

Throughout the surgery, the MAP and HR were measured at baseline (0 min), after induction, after intubation, and again after 5, 10, 20, 30, 40, 50 min. ET sevoflurane measures were recorded 5, 10, 20, 30, 40, 50 min into the surgery.

Esmolol (50 mcg kg^{-1} min^{-1}, IV, Group E) and lidocaine (2 mg kg^{-1} min^{-1}, IV, Group L) and saline (10ml h^{-1}, IV, Group C) infusions commenced immediately upon the beginning of the surgery and were maintained throughout the surgical procedure. All the drugs were prepared by a personal not involved in this study and the infusion pumps and syringes were covered with a dark sheath to maintain blindness and presented to the blind investigators. All surgical procedures were conducted by senior surgeons using the same techniques. Intraperitoneal pressure was maintained below 14 mmHg. Fifteen minutes before the final suturation, 0.2 mg kg^{-1} metaclopramid (IV) and 75 mg kg^{-1} diclophenac sodium (IM) were administered to all groups. Ten milliliters of 0.25% bupivacaine was infiltrated into the trochar incisions, including the fascia. After the last suturation, sevoflurane, nitrous oxide and drug infusions were stopped. Neuromuscular block was antagonized using 0.05 mg kg^{-1} neostigmin and 0.5 mg atropine sulfate. In both the

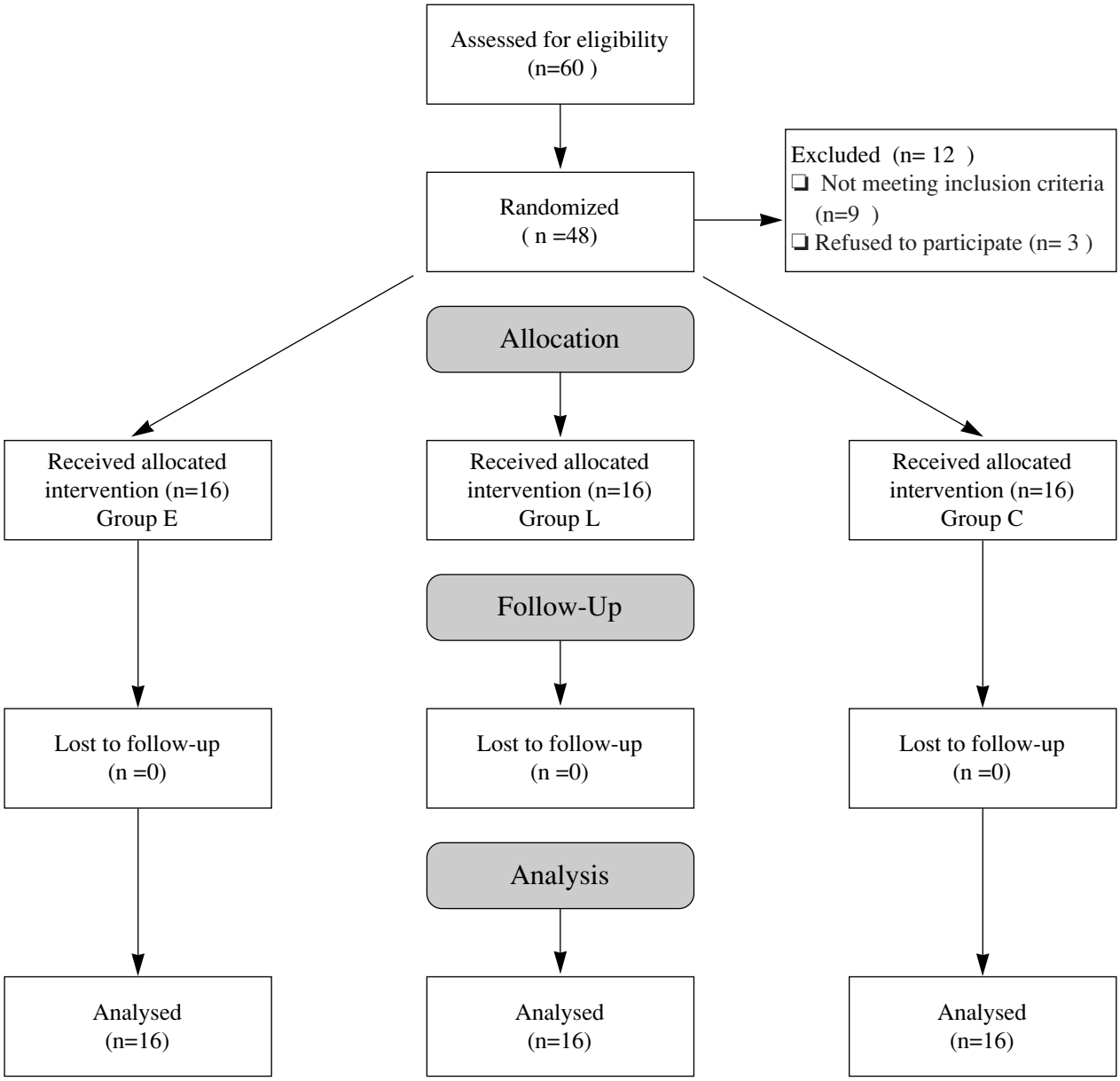

Figure 1: Flowchart of the study population (E, Esmolol; L, Lidocaine; C, Control)

post-anesthesia care unit (PACU) and the surgical ward, patients were examined by blinded anesthesiologists. Postoperative analgesia was induced using fentanyl (iv) with PCA (10 mcg bolus, 10 mcg h^{-1} basal infusion with a 10-min lockout period) and was administered for 24 hours (CADD-Legacy® PCA pump, Smiths Medical, USA). In the PACU, pain intensity was assessed by VAS scores (measured on a scale from 0 to 10, where 0 = no pain and 10 = worst pain imaginable) in 5-min intervals. Patients who fulfilled Aldrete score of 9 were transferred to the appropriate clinic (9) . PACU discharge times were recorded.

Diclophenac sodium (im) was administered three times a day for postoperative analgesia. In the surgical ward, VAS, nausea, vomiting, pain localization (incisional and shoulder pain) and patient satisfaction (yes or no) were recorded at 3, 6, 12 and 24 hours after surgery. After the 24-hour period, the total fentanyl consumption of each patient and the number of patients' exibiting first flatus by 24 h were calculated. Adverse drug effects (such as hypotension, dyspnea, bradycardia, urinary retention, itching, perioral numbness, visual disturbances, muscle twitching, agitation and dysarthria) were also noted. According to hospital protocols, patients were not discharged until at least 24 h after surgery.

Statistical Analysis

Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 11.5 software (SPSS Inc., Chicago, IL, United States). Shapiro-Wilk tests were used to test the normality of distributions of continuous variables. Data were expressed as the mean ± SD the standard deviation or median (interquartile range), where applicable. Nominal variables were expressed as the number of cases and percentages. Mean differences were compared using One-Way ANOVAs, and Kruskal Wallis tests were used to compare median values. When one-way ANOVAs or Kruskal Wallis tests revealed statistically significant differences, Tukey's or Conover's non-parametric multiple comparison tests were used to determine specific group differences. Nominal data were analyzed by Pearson's Chi-squared tests. Repeated Measures ANOVAs were used to evaluate hemodynamic parameters. P values less than 0.05 were considered to be statistically significant, and Bonferroni's adjustments were applied for all possible multiple comparisons to control for Type I error.

Power analysis indicated that sample sizes of at least 11 per group would be required to detect at least 250-mcg differences in postoperative fentanyl consumption between any two groups with a power of 95% at a 5% significance level. The difference of 250 mcg was taken from the literature (10).

RESULTS

A total of 48 randomized patients completed the study and were followed up for 24 hours in the related service. There were no significant differences in the demographic data or duration of surgery between the three groups. The mean intraoperative end-tidal sevoflurane concentrations were not significantly different between groups (p>0.05) (Table 1). In addition, no statistically significant differences in HR or MAP were observed between the groups at any of the measurement times (p>0.05) (Figure 2).

The postoperative VAS scores at the 10 min, 30 min and 3 h time points were lower in Group E than in Group C (p<0.05). However, there were no differences in VAS scores between the groups at the other measurement times (p>0.05) (Table 2). Fentanyl consumption in the PACU was 50±11 mcg for Group E, 75±18 mcg for Group L and 100± 27 mcg for Group C. All three groups had significantly different levels of fentanyl consumption in the PACU (p< 0.05). Fentanyl consumption over the 24 h immediately following surgery was 402±72 mcg in Group E, 728±86 mcg in Group L and 663±84 mcg in Group C. Patients in Group E consumed significantly less fentanyl than those in Group L and C (p=0.000). Moreover, the number of patients exhibiting first flatus by 24 h was 14 in Group E, 7 in Group L and 8 in Group C (p = 0.024). All groups exhibited similar levels of vomiting, nausea, shoulder pain, incisional pain, patient satisfaction and PACU discharge time (p>0.05) (Table 3). Drug-related side effects were not observed.

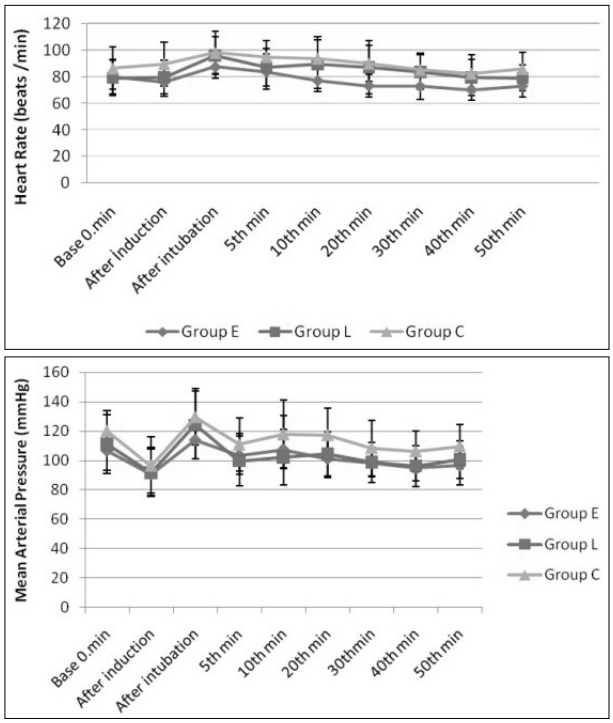

Figure 2: Changes in mean arterial pressure (MAP) and heart rates during surgery. Data are expressed mean ±SD

Table 1: Demographic Data and Perioperative Details: Values are mean ± SD, number, proporsion (%) or median (interquartil range).

	Group E n = 16	Group L n = 16	Group C n = 16	P
Age (years)	47±14	43±11	51± 14	0.332
Male/Female	3/13	3/13	4/12	0.881
Body Mass Index (kg m^{-2})	25 ± 3	26 ± 2	26 ± 3	0.777
Duration of surgery (min)	58 (42-94)	55 (35-80)	57 (41-105)	0.907
End-tidal sevoflurane (%)	1.7 ± 0.3	1.9 ±0.3	2 ± 0.4	0.098

Table 2: Postoperative VAS (Visual analog scale):Values are median (interquartile range).

	Group E n = 16	Group L n = 16	Group C n = 16	P
5.min	6(5-6)	6 (5-7)	7(6-7)	0.052
10.min	5(5-6)	6(5-7)	7(6-7)	0.006[a]
30.min	4(4-5)	6(4-6)	6(6-7)	0.001[a]
3.h	4(2-5)	5(2-6)	6(2-6)	0.006[a]
6.h	3(3-4)	4(3-5)	3(3-5)	0.454
12.h	2(1-2)	3(2-4)	2(1-4)	0.282
24.h	1(0-2)	2(0-3)	1(0-3)	0.357

[a] : Difference between Group E and Group C

Table 3: Postoperative Conditions :Values are mean ± SD , numbers (n), proportion (%) or median (interquartil range)

	Group E n = 16	Group L n = 16	Group C n = 16	P
PACU Discharge time (min)	11±8	12±6	11±9	0.453
Fentanyl consumption (mcg) in PACU	50 ±11	75±18	100±27	0.000[a,b,c]
Fentanyl consumption(mcg) Total	402±72	728 ± 86	663 ±84	0.000[a,b]
Number of PCA request	18(10-29)	32(17-39)	29(19-40)	0.154
First flatus in 24 h (n) (%)	14(87.5%)	7(43.8%)	8(50%)	0.024[a,b]
Nausea (n) (%)	5 (31.3%)	8 (50.0%)	10 (62.5%)	0.205
Vomiting (n) (%)	1 (0.6%)	1 (0.6%)	0 (0%)	0.352
Patient satisfaction rate				0.378
Poor	1 (6.3%)	2 (12.5%)	1 (6.3%)	
Good	15 (93.7%)	14 (87.5%)	15 (93.7%)	
Shoulder pain (n) (%)	3 (18.8%)	3 (18.8%)	2 (12.5%)	0.855
Incisional pain (n) (%)	5 (31.3%)	7 (43.8%)	11 (68.8%)	0.097

[a] : Difference between Group E and Group L
[b]: Difference between Group E and Group C
[c]: Difference between Group L and Group C

Discussion

The present study demonstrates that fentanyl consumption is decreased over the 24 h following laparoscopic cholecystectomies by intraoperative 50 mcg kg^{-1} min^{-1} esmolol infusions but not by infusions of 2 mg kg^{-1} min^{-1} lidocaine and saline. Although the esmolol, lidocaine and control groups showed similar side effects, more patients in the esmolol group exhibited flatus by 24 h than patients in Groups L or C.

Esmolol is an ultra-short-acting selective β_1 blocker that is frequently used in intensive care units and during surgeries (11). Several previous studies have demonstrated hypnotic, analgesic and amnestic effects of esmolol, in addition to its primary effects on the sympathetic nervous system (12-14). The decreased postoperative pain observed with esmolol treatment has been attributed to its intrinsic analgesic effects. β blockers cause a decrease in hepatic metabolism of opioids and thereby result in a reduction in opioid tolerance and increased analgesia (7-12). Esmolol has been shown to activate G protein signaling in isolated cell membranes. G-protein coupled receptor agonists inhibit neurotransmitter release via presynaptic (voltage-gated Ca^{2+}) or postsynaptic (potassium) channels (15). In rats, β blocker administration has been shown to decrease pain-related behaviors following intrathecal formalin injections (16).

Throughout those mechanisms clinical studies have concluded that esmolol exhibits analgesic effects. In addition, several studies have demonstrated a decrease in intraoperative anesthetic need and postoperative opioid consumption after esmolol infusions during hysterectomies and laparoscopic cholecystectomies (12, 17). In contrast, Berkenstadt et al (18) concluded that esmolol (80 mg during induction) had no effect on anesthesia

depth in arthroscopy patients based on BİS monitoring. The lack of effect of esmolol in this study was attributed to the fact that esmolol is a peripherally acting drug that cannot cross the blood brain barrier and thus cannot alter EEG waves. This result is in accordance with our study, which demonstrated that although intraoperative anesthetic need was similar in Groups E, L and C, postoperative fentanyl consumption in both the early and late postoperative periods was reduced in Group E compared to the other groups.

Lidocaine has both analgesic and anti-hyperalgesic effects. This property is explained through its anti-nociceptive effect of inhibiting primary evoked postsynaptic reflexes by sodium channel blockers in the dorsal horn of the spinal cord (19). Hollmann et al (20) have also shown that lidocaine has a role in the modulation of inflammatory response processes and that its anti-inflammatory effects may contribute to the postoperative analgesia observed after lidocaine treatment. The frequently used local anesthetic, lidocaine, has been shown to induce effective postoperative analgesia, decrease opioid consumption and promote rapid recovery (21). In contrast, Groudine et al (22) reported that decreased opioid consumption only occurred in early postoperative period and that total opioid consumption and additional opioid usage was not changed by lidocaine administration. In agreement with this previous study, although fentanyl consumption in Group L at the PACU was reduced compared to controls, total fentanyl consumption was similar in the control group and in Group L.

Lidocaine is generally considered to be a safe drug, but it has several side effects, including peri-oral numbness, drowsiness, diplopia, muscle twitching, euphoria and agitation (5,6). These unwanted side effects are typically dose related, and patients with hepatic and cardiac problems are more prone to these effects (23). We did not observe any of those complications in the current study using a 2 mg kg^{-1} h^{-1} lidocaine infusion dose.

The normalization of intestinal motility is very important in postoperative recovery. Opioid consumption for postoperative analgesia, visceral inflammation secondary to surgery and postoperative sympathetic stimulation were major factors in the recovery of intestinal motility. Lidocaine (IV) has been reported to maintain intestinal motility by decreasing postoperative opioid consumption, directly inhibiting the sympathetic mesenteric plexus and exhibiting an anti-inflammatory effect (24). In contrast, Wu et al (25) did not observe a recovery of intestinal motility using a 3 mg kg^{-1} h^{-1} lidocaine infusion. They hypothesized that these inconsistent effects of lidocaine might be explained by differences in drug doses and surgical procedures. In the previous study, the number of patients exhibiting flatus by 24 h was similar in the control group and the lidocaine group.

We are unaware of any previous clinical or in vitro studies regarding the effects of esmolol on intestinal recovery. In our study, we observed an earlier recovery of intestinal activity in patients treated with esmolol compared to control patients and patients treated with lidocaine. We hypothesize that this effect can be explained by the reductions in opioid consumption and intestinal sympathetic blockade observed after esmolol infusion. In vitro studies have revealed β_1, β_2 and β_3 receptor expression in intestinal muscle (26). Adrenergic blockers are thought to increase intestinal motility in healthy individuals under a variety of clinical situations, but probable systemic side effects have limited their use (27). Future studies will likely explain the mechanisms through which esmolol promotes rapid intestinal recovery.

One limitation of our study is the fact that we were unable to use BIS to monitor the depth of anesthesia. In addition, it is possible that the inclusion of ASA III-IV patients would have yielded important additional information, especially for assessing the side effects related to lidocaine.

Although neither adjuvant delayed PACU discharge, esmolol infusions (50 mcg kg^{-1} min^{-1}), unlike lidocaine infusions (2 mg kg^{-1} min^{-1}), decreased the postoperative 24 h opioid consumption compared to controls. In conclusion, esmolol might be a useful adjuvant for postoperative opioid spare and early recovery of bowel function following laparoscopic cholecystectomies.

The authors declared that there is no conflict of interest.

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