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Case Report

Labetalol as an Alternative to Esmolol and Fentanyl for Maintaining Hemodynamic Stability during Laparoscopic Surgery: Comparative Effects on Recovery Profiles and a Literature Review

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Abstract

β-blockers like labetalol and esmolol have been successfully used for controlling acute autonomic responses during surgery.

Objective: To compare the intraoperative use of labetalol and esmolol to fentanyl for maintaining hemodynamic stability during laparoscopic surgery and assess their effects on recovery profiles.

Methods: 75 patients were randomly assigned to receive one of three different adjunctive treatments regimens. Immediately prior to induction of anesthesia, 1 mL of the unlabeled study medication (fentanyl [50µg/mL], or labetalol [5mg/mL], or esmolol [10 mg/mL]) was administered. A second 1mL dose of the same study medication was administered immediately before skin incision and subsequently as needed [‘rescue’] during the surgical procedure to maintain heart rate (HR) and mean arterial pressure within 15% of the pre-induction baseline values.

Results: The labetalol and esmolol groups had similar intraoperative HR and MAP values compared to the fentanyl group (p=0.4 and p=0.1 respectively). Fewer patients in the labetalol group required intraoperative rescue medications compared to the esmolol and fentanyl groups (p=0.0003). There were no significant differences in the requirement for parenteral opioid medication in the early postoperative period among the three groups. Of the post-discharge recovery outcomes studied, only incidence of ‘low appetite’ differed among the three groups, favoring the labetalol group over the fentanyl group (p=0.05). Labetalol was also less costly than both esmolol and fentanyl.

Conclusion: Labetalol and esmolol were found to be comparable to fentanyl for maintaining hemodynamic stability during laparoscopic surgery. However, labetalol required less intraoperative rescue medication and had less adverse effect on appetite in the post-discharge period.

Keywords: Esmolol; Labetalol; Fentanyl; Opioid-sparing; Recovery outcomes

Main Points

- Beta-blockers can control acute autonomic responses during surgery
- Beta-blockers can be used as alternatives to opioids during surgery
- Labetalol is a cost-effective alternative to both esmolol and fentanyl

1. Introduction

Although many different anesthetic adjuvants have been used for the prevention and treatment of acute hemodynamic responses during laparoscopic surgery [1-7]. Fentanyl remains the most commonly used drug. Given the role of fentanyl in the current opioid epidemic [8], cost-effective non-opioid alternatives are clearly needed [9]. Use of non-opioid analgesics acting at different sites within the central and peripheral nervous systems is a well-documented approach to improving postoperative pain management and reducing opioid usage leading to a faster recovery following surgery [10-13].

β-blocking drugs can potentially modify adrenergic-mediated pain pathways [14] by activating G-proteins in cellular membranes, a property shared with the alpha-2 agonist/antagonists like clonidine and dexmedetomidine (which also produce centrally-mediated analgesia) [15]. Inhibitory G protein-coupled receptor agonists act upon post-synaptic inhibition via G protein-coupled potassium channels or via the pre-synaptic inhibition of neurotransmitter release through the regulation of voltage-gated Ca2+ channels to produce an antinociceptive effect [16-17]. β-adrenergic blocking drugs also decrease their own metabolism and drugs like fentanyl by reducing liver blood flow [14]. Esmolol is a cardio-selective ultrashort-acting β-blocker with moderate lipophilicity that can be involved in the modulation of central adrenergic activity, [18] and has an elimination half-life of ~9 min after either a bolus or continuous infusion. Labetalol is a selective alpha-1 and non-selective β-receptors blocker with a ratio of alpha: β of 1:7. Labetalol maximum (peak) action occurs <5 min and it has a duration of action of ~2-4 hr which may provide advantages over a short-acting drug like esmolol. Labetalol is also one-tenth the cost of esmolol based on the usage requirement) [19-20].

There is evidence to support the use of esmolol and labetalol to: [1-7, 11-18, 21-29] a) control transient acute autonomic responses during intubation/extubation and throughout the surgical procedure, b) reduce the anesthetic requirement during both propofol and volatile anesthesia, c) decrease opioid intraoperative opioid consumption d) as an alternative to the use of intraoperative opioids, 2 e) facilitate a faster emergence from anesthesia, f) improve pain scores g) decrease opioid consumption in the postanesthesia care unit (PACU), h) improve perioperative outcomes by reducing opioid-induced side effects as such as pruritus, constipation, ileus, nausea and vomiting (PONV), and i) shorten the length of the hospital stay. For example, Zaugg et al. reported that, in elderly patients undergoing major non-cardiac surgery, perioperative β-blockade with atenolol improved hemodynamic stability, reduced the opioid analgesic requirement, and contributed to a faster early recovery [7].

The primary hypothesis being tested in this study was that the use of labetalol as an alternative to esmolol and fentanyl during a laparoscopic surgery would result in comparable control of acute intraoperative autonomic response while reducing the perioperative requirement for opioid analgesics. The secondary objectives of the study were to determine the effect of these sympatholytic drugs (vs. fentanyl) on the intensity of postoperative pain and opioid-related side effects in the early postoperative period, the time to resume activities of daily living after discharge home and recovery profiles.

2. Methods

This clinical study was approved by the ethics committee of Cedars-Sinai Medical Center in Los Angeles, CA [Institutional Review Board (IRB)], ethical committee (Protocol) no. Pro00019328 on September 2009. The study was registered with ClinTrials.gov (Reg. # NCT01114971). It also complied with all 25 items on the Consort 2010 checklist. After obtaining IRB approval and written informed consent, 75 adult patients scheduled to undergo

laparoscopic abdominal surgical procedures under general (endotracheal) anesthesia were enrolled in this study and randomly assigned to one of three treatment groups: Labetalol (n=25), Esmolol (n=25) or Fentanyl (n=25). Randomization assignment was generated with a 1:1:1 allocation ratio using a computer software program. The randomization number specifying the study medication (namely, Labetalol, Esmolol or Fentanyl) was placed in sealed envelope and given to the staff anesthesiologist on the day of the scheduled procedure after completing the patient's preoperative assessment. The study medication was drawn up in a 5-mL plastic syringe (labelled Study Drug) by one of the co-investigators who were not involved in the intraoperative management of the study patients. The anesthesiologists caring for the study patient, the investigator collecting data, and the patients were all blinded as to the contents of the syringe containing study medication.

Prior to the day of the surgery, potential study subjects received a packet of information about the study from the research team. This packet contained an invitation letter (initial patient contact letter), HIPAA form and informed consent form describing the study in lay terminology. Subjects who were interested in participating in the study were asked to bring the material to the hospital on the day of the surgery. In the preoperative holding area, one of the investigators explained the details of the study and checked to make sure that the subject met all inclusionary criteria and then they were invited to sign the consent documents. All subjects provided a detailed medical history including demographic information (e.g. age, weight, height, ethnic origin, smoking history, drug usage, and previous PONV).

Inclusionary criteria included: 1) Patients undergoing laparoscopic abdominal surgical procedures. 2) Willingness and ability to sign an informed consent document. 3) No allergies to the medications used for the scheduled operation. 4) 18-80 years of age. 5) ASA Class I – III. 6) Adults of either gender. Exclusionary criteria included: 1) known allergy, hypersensitivity or contraindications to anesthetic or analgesic medications. 2) A clinically-significant medical conditions, such as brain, heart, kidney, endocrine, or liver diseases, peptic ulcer disease or bleeding disorders. 3) Pregnant or lactating women. 4) History of alcohol or drug abuse within the past 3 months. 5) Any other conditions or use of any medication which may interfere with the conduct of the study such as overt cardiac failure, greater-than-first-degree heart block, severe bradycardia, cardiogenic shock, severe hypotension, anyone with a history of obstructive airway disease including asthma, and hypersensitivity to the study drugs. Withdrawal criteria included the following items: 1) Bradycardia, hypotension, allergies, hypersensitivity or contraindications to medications which were part of the standardized anesthetic protocol. 2) Clinically-significant medical conditions.

Upon arrival in the operating room, standard monitoring devices were applied, including an automatic blood pressure cuff, three-lead electrocardiogram, capnograph, pulse oximeter, and bispectral (BIS) index monitor. Patients with anxiety were premedicated with midazolam 2 mg. A standardized anesthesia technique was administered to all three study groups consisting of propofol, 1-2 mg kg^{-1} IV and lidocaine 30-70 mg IV, for induction, succinylcholine 1-1.5 mg kg^{-1} was used to facilitate tracheal intubation, and desflurane 3% inspired in oxygen (3 L min^{-1}) in combination with a propofol infusion at 75 µg kg^{-1} min^{-1} in for maintenance of anesthesia and to maintain a BIS value of 40-60. The "blinded" study medication was prepared in an unlabeled 5-ml syringe identified with the patient's name and study number by a co-investigator who was not involved in patient's anesthetic management. The study medication solution contained either fentanyl 50 µg per mL (Group 1), labetalol 5 mg per mL (Group 2), or esmolol 10 mg per mL (Group 3) and was administered in the following sequence: (a) 1 ml at the time of induction [immediately prior to propofol] (excluding patients with hypotension or bradycardia), (b) 1 ml at the time before surgical incision (1 min prior to incision), and (c) 1-2 ml boluses as needed ('rescue') during the operation to maintain hemodynamic stability (MAP within 15% of the pre-induction baseline value, and/or HR between 60 and 90 bpm). The indication to use 1 or 2 ml was left to the anesthesiologist criterial base on MAP and/or HR value. Fentanyl was used to provide intraoperative analgesia and for prophylaxis of postoperative pain as anesthesiologists discretion.

A nondepolarizing skeletal muscle relaxant was administered to maintain the intraoperative neuromuscular block. Ondansetron, 4 mg IV, and dexamethasone, 4 mg IV, were given before the end of surgery for antiemetic prophylaxis. Ketorolac 30 mg was given as a preventative analgesic 15-30 min prior to the end of the surgery. Local anesthesia (0.5% bupivacaine) was injected at all incision sites for local analgesia by the surgeon.

The maintenance anesthetic drugs were discontinued upon completion of skin closure. After awakening from anesthesia (eye opening) and tracheal extubation, the patient was transferred to the PACU. The White fast-track score [30] was assessed immediately upon arrival to PACU and at 1- to 5-min intervals until they achieved a score > 12. Patients were discharged from the PACU when they satisfied the standardized Aldrete PACU discharge criteria [31]. In the PACU, if the patient complained of pain hydromorphone, 0.1–0.2 mg IV boluses, was administered to manage the surgical pain. The discharge criteria included being awake and alert with stable vital signs, possessing the ability to ambulate, passage of urine, and absence of intractable side effects (e.g. pain, dizziness, or PONV).

The standardized perioperative evaluations included the following:

1. Vital signs [including MAP, HR, respiratory rate (RR), end-expiratory carbon dioxide, and SpO2] were recorded at 5- to 10-min intervals throughout the intraoperative period and at 15-30 min intervals in the PACU until discharged.
2. Bispectral index monitor units.
3. Dosages of all anesthetic drugs, local anesthetics, and IV fluid therapy during the operation, including any repeat doses of the study medication.
4. Times of duration of surgery (from skin incision until closure) and anesthesia (from IV induction until discontinuation of the anesthetic drug).
5. Recovery times (from discontinuation of anesthetic drugs until eye opening, following verbal commands and orientation), time to achieving a White's fast-track score > 12 and time to meeting the Aldrete standardized discharge criteria ('home readiness').
6. VRS scores for pain and the presence of nausea: assessed immediately prior to receiving the study medication ('baseline) and at 30-min intervals during the PACU stay.
7. Requirements for 'rescue' analgesic and antiemetic medication in the PACU, as well as any side effects occurring prior to being discharged.

Prior to discharge home, each patient received a pain and nausea diary and a copy of a questionnaire with questions regarding postoperative outcomes and they were reminded that a telephone interview was going to be conducted approximately 4 weeks after surgery by one of the investigators to assess: the maximum pain VRS score, amount of pain medication taken, incidence of nausea-vomiting, antiemetic medication required, and the Quality of recovery (QoR) scores [32]. Global evaluation of anesthesia experience, with 0= poor, 10= excellent, later recovery profiles, resume normal, physical activities, recovery of normal bowel & bladder function, return to normal energy level, able to return to work, pain at the incision site, any side effects following discharge and the worst aspect of the recovery process.

2.1 Statistical analysis

In a single factor ANOVA study, a sample size of 25 patients in each group whose means were to be compared is determined by power analysis based on the assumption that the time to return to feeling normal will be reduced by 2 days in the labetalol group and esmolol group compared to the fentanyl group. The total sample of 75 subjects achieves 95% power using the Tukey-Kramer (Pairwise) multiple comparison test at a 0.05 significance level and a SD of 1 [33].

The analysis was performed using SAS 9.3 for Windows (SAS Institute, Cary, NC, USA) and R. 3.0.1. Our dataset contained both categorical and continuous measurements. For categorical measures, we presented total numbers (n) with the percentages (%) and used Chi-square test (or Fisher's exact test) to conduct the group comparisons. For continuous measures, we presented mean values with their standard deviations and used the Kolmogorov-Smirnov test to check the normality. To conduct the multiple comparisons among those 3 groups, we performed the one-way ANOVA if the measure is approximately normal and the Kruskal Wallis test if the measure fails to pass the normality test, and when a significant difference was found, a Mann-Whitney U test was used for *post hoc* comparisons between the intergroups. A Bonferroni correction was applied when multiple comparisons were performed over time. All tests

were two-sided; and P values ≤ 0.05 were considered statistically-significant. Data are presented as mean values ± SD, numbers (n), and percentages (%).

3. Results

A total of 75 consenting patients successfully completed the study. The three groups were comparable with respect to demographic characteristics, history of drug or alcohol use, smoking, procedures type, premedication and intraoperative drugs administered. (Table 1) The fentanyl group received a total of 186±79 µg, labetalol 20 ± 9 mg and esmolol 66 ± 31 mg.

	Labetalol (n=25)	**Esmolol** (n=25)	**Fentanyl** (n=25)	**p value**
Age (yr)	42 ± 14	49 ± 11	46 ± 13	0.106
BMI (kg/m^2)	37 ± 7	39 ± 8	35 ± 7	0.186
Gender (n) F/M	21/4	15/10	21/4	0.072
ASA (n) I/II/III	2/3/20	1/3/21	3/8/14	0.189
Race (n) Asian/Black/Caucasian /Other	0/6/19/0	1/4/19/1	3/3/19/0	0.362
Smoker (n) yes/no	3/22	2/23	3/22	0.869
Alcohol user (n) yes/no	11/14	8/17	8/16	0.628
Motion sickness (n) yes/no	6/19	3/22	4/23	0.250
PONV (n) yes/no	7/18	1/24	6/19	0.066
Premedication: Midazolam 2 mg (n)	20	14	16	1.180
Intraoperative drugs				
Lidocaine mg	53 ± 21	47 ± 20	51 ± 20	0.882
Propofol Induction (mg)	214 ±57	227 ± 69	215 ± 54	0.899
Propofol Infusion (mg)	581 ± 301	631± 313	503 ± 218	0.310
Propofol total (mg)	804 ± 312	864 ± 361	724 ± 238	0.396
Succinylcholine (mg)	107 ± 23	118 ± 36	108 ± 28	0.540
Fentanyl (ug)	0	0	186 ±79	
Labetalol (mg)	20 ± 9	0	0	
Esmolol (mg)	0	66 ± 31	0	
Required rescue medication (n)	8†‡	22	15§	0.0003*
Hydromorphone (n)	5	3	4	0.645
Ketorolac 50mg (n)	14	13	10	0.259
Ephedrine (n)	2	4	3	0.776
Phenylephrine (n)	0	1	3	0.248
Hydralazine (n)	2	4	3	0.321
Glycopyrrolate (mg)	0.57 ± 0.2	0.5 ± 0.2	0.48 ± 0.3	0.106
Neostigmine (mg)	3.3 ± 0.9	3.1± 0.9	2.8 ± 1.2	0.200
End-tidal Desflurane (%)	3± 0.9	3± 0.8	3± 0.5	0.103
Total IV Fluids (mL)	1572 ± 518	1661 ± 615	1511 ± 517	0.554

Table 1: Demographic Characteristics and Intraoperative Drugs Used in the Three Treatment Groups

Numbers (n), Mean values ± SD (standard deviation); * p-value < 0.05 between the 3 groups; † p-value <0.05 Labetalol vs. Esmolol; ‡ p-value < 0.05 Labetalol vs. Fentanyl; § p-value < 0.05 Esmolol vs. Fentanyl

The intraoperative open label fentanyl provided for analgesia and/or for prophylaxis of postoperative pain per anesthesiologists discretion was: Fentanyl group n=6 [total dose from 50-200µg], labetalol group n=4 [total dose from 50-150µg], and esmolol group n=5 [total dose from 50-250µg]. All three study groups had similar' intraoperative HR and MAP values. However, the labetalol group required significant fewer intraoperative boluses of rescue medication (p=0.0003).

The type of surgery, duration of anesthesia/surgery, intraoperative vital signs, recovery variables, PACU stay, side

effects, rescue analgesic, and pain scores at PACU did not differ among the three treatment groups (Tables 2 and 3). Table 4 summarizes the post-discharge recovery outcome data, time to resumption of normal activities of daily living, quality of recovery score, the factors interfering with return to normal activities did not significantly differ among the three groups; however, patients in the Fentanyl group experienced a significantly higher incidence of low appetite after discharge home compared to the Labetalol group [$p<0.05$] (Table 4). Based on local pharmacy information Labetalol ($0.18 - $1.56/ml) was also less costly than esmolol and fentanyl ($2.56/ml and $1.25/ml respectively) [34] (Table 5).

	Labetalol (n=25)	**Esmolol** (n=25)	**Fentanyl** (n=25)	**P value**
Procedures				
Cholecystectomy	6	5	9	0.412
Gastrectomy sleeve	5	4	4	0.911
Gastric band placement/removal	7	4	5	0.573
Gastric bypass	7	12	7	0.230
Intraoperative times				
Anesthesia time (min)	108 ± 33	129 ± 42	117 ± 40	0.190
Surgery time (min)	84 ± 30	106 ± 40	94 ± 39	0.132
Extubation time (min)	5 ± 3	6 ± 5	5 ± 5	0.824
Intraoperative Vital Signs				
ETCO2 (mm Hg)	35 ± 3	34 ± 3	35 ± 3	0.889
SPO2 (%)	98.8 ± 1.1	98.5 ± 0.9	98.8 ± 0.9	0.404
Oxygen saturation L/min	4.3 ± 0.8	4.4 ± 0.8	4± 0.9	0.530
BIS (U)	37 ± 5	40 ± 6	41 ± 9	0.203
MAP (mmHg)	86 ± 8	88 ± 8	83 ± 8	0.122
Heart Rate (beats/min)	83 ± 9	85 ± 10	81± 10	0.351

Table 2: Procedures, Duration of anesthesia/surgery, and vital signs of the 3 treatment groups
Numbers (n), Mean values ± SD (standard deviation); * p-value < 0.05 between the 3 groups

	Labetalol (n=25)	**Esmolol (n=25)**	**Fentanyl (n=25)**	**p value**
Spontaneous eyes opening (min)	6 ± 4	6 ± 4	6 ± 4	0.851
Response to verbal commands (min)	7 ± 4.6	7 ±5	7 ± 5.4	0.891
Orientation to person and place (min)	10 ± 4	9.7 ± 6	9.3 ± 6	0.505
PACU Stay (min)	120 ± 63	140 ± 80	138 ± 76	0.586
Side Effects Nausea (n)	3	6	8	0.236
Vomiting (n)	1	1	1	-
Respiratory (n)	0	0	0	-
Itching (n)	0	0	1	-
Urine retention (n)	0	0	0	-
Rescue analgesic requirement: Opioids (n)				
Hydromorphone (mg)	1.1 ± 0.7	1.4± 0.9	1.5 ± 0.9	0.459
Lortab/Norco (n)	0	2	1	-
Ketorolac mg (n)	4	2	4	0.435
Ondansetron (n)	4	8	7	0.738
Labetalol (n)	2	2	1	0.441
Pain verbal rating scale in PACU (0=none to 10=intolerable)				
Pain on arriving in PACU	3.9 ± 3.5	4.6 ± 3.8	4.7 ± 3	0.740
Pain after 30 min	5.9 ± 2.8	5 ± 3	4.7 ± 3	0.576
Pain after 60 min	3.6 ± 2.6	4.5 ± 2.2	3.7 ± 2	0.445
Pain after 90 min	3 ± 3	3.9 ± 2.5	3.2 ± 2	0.576

Table 3: Recovery variables, PACU stay, Side effects, Rescue Analgesic, and Pain scores at PACU
Numbers (n), Mean values ± SD (standard deviation); * p-value < 0.05 between the 3 groups

	Labetalol (n=25)	Esmolol (n=25)	Fentanyl (n=25)	P value
Experienced pain at home (n)	16	15	17	0.572
Highest VRS (0=none to 10=intolerable)	5.7 ± 3	5.4 ± 2	5.5 ± 2	0.850
Used pain medication (n)	14	13	15	0.852
Experienced lingering sensation (n)	11	6	8	0.281
Nausea (n)	7	6	8	0.825
Used nausea medication (n)	3	3	3	-
Vomiting (n)	4	3	4	0.835
Constipation (n)	15	12	12	0.463
Dizziness (n)	5	4	7	0.486
Fatigue (n)	12	11	11	0.852
Sleepiness (n)	10	11	11	0.940
Headache (n)	4	6	6	0.761
Low Appetite (n)	7‡	9	15	0.050*
Time to recover a normal:				
Bladder function (days)	1.5 ± 0.8	1.4 ± 0.7	1 ± 0.2	0.686
Bowel Function (days)	5.7 ± 6	7.8 ± 8.7	4.7 ± 6	0.270
Sleep pattern (days)	5.3 ± 8	7.6 ± 9	5.4 ± 9	0.168
Energy level (days)	12 ± 11	14 ± 11	14 ± 11	0.880
Time to feeling normal (days)	10 ± 9	12 ±10	11 ± 9	0.920
Pain at the incision site (days)	7 ± 9	8 ± 8	9 ± 9	0.586
Quality of recovery score	15 ± 3	16 ± 2	15 ± 3	0.785
Major factor interfering with return to normal activities				
None	5	4	5	0.915
Fatigue	4	9	7	0.202
Pain	7	5	6	0.803
Discomfort	1	2	0	-
Limited Movement	2	0	4	-
Lifting	1	1	0	-
Doctor's Order	2	3	0	-
Other	1	1	1	-
Satisfaction of the pain management ¥	9± 1.2	8±2.5	9.1±1.6	0.171
How clear were with the recommendation for the pain control at home¥	9.5 ±0.9	9.5 ±0.9	9.7 ± 0.8	0.496

(0=worst to 10=Best) ¥

Table 4: Follow up one month after discharge home in the three treatment groups

Numbers (n), Mean values ± SD (standard deviation); * p-value < 0.05 between the 3 groups; ‡ p-value < 0.05 (0.02) Labetalol vs. Fentanyl

	LABETALOL	ESMOLOL	FENTANYL
Onset of action	2-5 minutes	60 seconds	1-2 minutes
Peak effect	5 to 15 minutes	2 to 6 minutes	20-30 minutes
Duration	~2-4 h	10-30 minutes	0.5-2 hour
Half-life elimination	~5.5 hours	9 minutes	2 to 4 hours
Price	5 mg per mL mL price: $0.18 - $1.56	100 mg per 10 mL mL price: $2.56	100 µg per 2 mL mL price: $1.25

Table 5: Pharmacokinetics and pharmacodynamics of Labetalol, Esmolol and Fentanyl

4. Discussion

In light of the current opioid crisis, anesthesiologists are increasingly utilizing multimodal ('balanced') analgesic therapies, as part of an integrative approach to managing perioperative pain [8]. Opioid-free anesthesia (OFA) is a technique where no intraoperative systemic, neuraxial or intracavitary opioid is administered during surgery [35-37]. Ideally, OFA would also minimize opioid use in the postoperative period. Apart from the current opioid epidemic, there are other compelling reasons to avoid excessive use of opioid analgesics in the ambulatory surgery setting (e.g., minimizing nausea and vomiting, ileus, urinary retention). In an attempt to reduce pain scores, opioid usage and adverse side effects, and achieve a faster recovery following elective ambulatory surgical procedures, we studied a multimodal approach using beta-blocking drugs to maintain an intraoperative hemodynamic stability. Methods involving the use of non-opioid analgesics to minimize postoperative pain should decrease opioid-related complications and potentially reduce overall healthcare costs. Beta-blockers have been administered for the management of postoperative pain, to reduce perioperative cardiac complications, to reduce the stress response and decrease opioid requirement and pain score following surgery [5-6,21,38-44]. Esmolol and labetalol have found to be effective in attenuating the acute hemodynamic response to laryngoscopy, intubation and extubation [12,16,24]. The intraoperative administration of labetalol and esmolol have reduced the intraoperative and postoperative opioid requirements, decreased the desflurane anesthetic requirement, reduced pain scores in the early postoperative period, prolonged the time to the first request for analgesic medication, while also providing a better hemodynamic stability, improved surgical visibility, decreasing the amount of intraoperative and postoperative blood loss and even reduced the surgical time [27,41].

In patients undergoing laparoscopic abdominal surgery, perioperative administration of esmolol has been shown to reduce the anesthetic requirement, decrease perioperative opioid use and the incidence of PONV, leading to an earlier discharge from hospital and improved patient satisfaction [2,5,25,29,38-40,45-47]. However, not all authors have reported these same advantages when using beta-blocking drugs during the intraoperative period [48-49]. While there are several published studies, which have focused on the analgesic effects of esmolol in patients undergoing laparoscopic abdominal surgery, there are no peer-reviewed publications describing the use of labetalol in this clinical setting. In the present study, intraoperative administration of labetalol, like esmolol, was an effective alternative to fentanyl for maintaining hemodynamic stability during laparoscopic surgery. Regarding the intraoperative use of opioid analgesics, this study revealed that the Control group received 186±79 μg of fentanyl (vs. none in the Esmolol and Labetalol groups) as part of standard of care. In addition, 6 patients in the fentanyl (Control) group required fentanyl rescue [dosages from 50-200 μg] compared to 4 in the Labetalol group [dosages from 50-150 μg] and 5 in the Esmolol group [dosages from 50-250 μg]. The use of the beta-blocking drugs esmolol and labetalol achieved comparable intraoperative hemodynamic stability as the control group receiving standard doses of fentanyl. Beta blockers decrease the requirement of opioids in part by decreasing hepatic metabolism of drugs like fentanyl which are dependent on liver blood flow [14]. The antinociceptive effect of labetalol may also be related in part to its potentiating effect on GABAergic transmission [50] and both of the beta-blockers effect the hippocampal β-adrenergic receptors, thereby blunting the contribution of β-adrenergic activation to the nociceptive process [18]. Although both labetalol and

esmolol achieved similar intraoperative hemodynamic values as fentanyl (p=0.4 and p=0.1 respectively), the labetalol group required significant less intraoperative opioid (fentanyl) rescue medication (p=0.0003). The reduced need for boluses of intraoperative rescue medication in the labetalol group may have been the result of its longer duration of activity compared to esmolol. These findings also support the findings of Coloma et al., [1] who reported that esmolol was an effective alternative to the ultra-short-acting opioid remifentanil for maintaining hemodynamic stability in patients undergoing outpatient gynecological laparoscopic surgery.

In reviewing the peer-reviewed literature regarding the use of beta-blocking drugs during laparoscopic abdominal surgery, there are several relevant articles. For example, Lee et al. [29] administered esmolol (0.5 mg kg^{-1}bolus followed by a continuous infusion of 10 µg kg^{-1} min^{-1}) during laparoscopic cholecystectomy, and when compared to ketamine (bolus of 0.3 mg kg^{-1}, followed with a continuous dosage of 3 µg kg^{-1} min^{-1}), esmolol was found to produce a greater reduction in the opioid requirement and pain scores in the early postoperative period after a remifentanil-based anesthesia. López-Álvarez et al., [5] administered a bolus of esmolol 0.5 mg kg^{-1} IV at induction followed by an infusion of 5-15 µg kg^{-1} min^{-1} to patients undergoing laparoscopic cholecystectomy and concluded that the use of intraoperative esmolol infusion reduced the morphine requirements and provided more effective postoperative analgesia compared to an infusion of remifentanil and ketamine [5]. In a prospective, randomized, observer-blinded study, Collar et. al., [2] compared an esmolol infusion [5-15 µg kg^{-1} min^{-1}] to either intermittent boluses of fentanyl or a continuous infusion remifentanil [0.1-0.5 µg kg^{-1} min^{-1}] on postoperative opioid requirements, side effects, and discharge time in patients undergoing ambulatory laparoscopic cholecystectomy. These authors concluded that an intraoperative IV infusion of esmolol contributes to a significant decrease in the requirement for postoperative opioid (fentanyl) administration for pain control, and in the need for ondansetron to treat PONV, thereby facilitating an earlier discharge home. [2] Dogan et at., [45] compared the effects of lidocaine (1.5 mg kg^{-1} min^{-1}) and esmolol (1 mg kg^{-1} min^{-1}) infusions on intraoperative hemodynamic changes, intraoperative and postoperative analgesic requirements, and recovery outcomes in adults patients undergoing laparoscopic cholecystectomy surgery. These authors concluded that lidocaine was superior to esmolol with respect to suppression of the hemodynamic responses to tracheal extubation, while esmolol was more advantageous than lidocaine with respect to speed of recovery from anesthesia and attenuation of early postoperative pain. Moon et. al.,[40] performed a randomized, double-blinded, placebo-controlled study evaluating the anesthetic and analgesic-sparing effect of esmolol (0.5 mg kg^{-1} bolus followed by an infusion of 30 µg kg^{-1} min^{-1}) during laparoscopic gynecological surgery and concluded that esmolol decreased both the sevoflurane anesthetic requirement and the need for postoperative fentanyl to treat pain in the early postoperative period. In our evaluation of post-discharge recovery outcomes, we found that patients in the fentanyl group experienced a significantly higher incidence of low appetite compared to the labetalol group. This finding is likely related to the well-known adverse effects of opioids on the gastrointestinal track (e.g., PONV and opioid-induced bowel dysfunction).

A potential limitation to this study was the lack of placebo group to the three active treatments for acute autonomic responses during the intraoperative period. Another criticism relates to the timing (24 hr or 7 days) of the follow-up evaluations of recovery outcomes after discharge home. These outcome assessments should have been performed at

more frequent intervals and in greater depth. Even though the protocol provided for the ability to titrate the rescue medication, the comparative dosages which were selected for the three study medications may have had an influence on the outcomes. More importantly, the small group sizes (n=25) limited our ability to assess differences in post-discharge outcomes which precluded to perform a more in-depth cost-benefit analysis.

5. Conclusion

Intraoperative use of labetalol is a cost-effective alternative to esmolol maintaining hemodynamic stability during laparoscopic surgery. Compared to esmolol, labetalol produced similar effects on opioid analgesic requirements and postoperative pain scores. Both of these beta-blockers can be used as alternatives to fentanyl during laparoscopy surgery procedures.

Key Messages

a. Beta-blockers can control acute autonomic responses during surgery as effectively as fentanyl.
b. Beta-blockers can be used as alternatives to opioids during laparoscopic surgery.
c. Labetalol is a cost-effective alternative to both esmolol and fentanyl.

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