Randomized, double-blind, placebo-controlled study of the analgesic effect of intraoperative esmolol for laparoscopic gastroplasty

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Research article

Keywords: Esmolol; postoperative analgesia; gastroplasty

Posted Date: August 9th, 2019

DOI: https://doi.org/10.21203/rs.2.12506/v1

Version of Record: A version of this preprint was published at Acta Cirúrgica Brasileira on January 1st, 2020. See the published version at https://doi.org/10.1590/s0102-865020200040000008.

Abstract

Background Patients undergoing bariatric surgery can have respiratory complications in addition to vomiting and ileus. Esmolol can decrease the consumption of opioids, reducing their side effects. The purpose of this study was to evaluate the analgesic effect of esmolol in patients allocated to laparoscopic gastroplasty. Methods Forty patients between 18 and 50 years old, of both genders, physical status ASA I-II, who underwent bypass gastroplasty were divided into two groups. Participants in group 1 received a 0.5 mg/kg bolus of esmolol in 30 mL of saline before induction of anesthesia, followed by infusion of 15μg/kg/min until the end of surgery; those in group 2 received 30 mL of saline bolus and infusion of solution in the same volume as group 1. The anesthesia included fentanyl (5ug/kg), propofol (2-4 mg/kg), rocuronium (0.6 mg/kg), 50% oxygen without nitrous oxide and 2% sevoflurane, with remifentanil if necessary. There were evaluated: remifentanil consumption, time to analgesic supplementation, pain intensity for 24 h and morphine dose over 24 h. Side effects were noted. Results Intraoperative remifentanil supplementation, time to recovery, and postoperative morphine supplementation were lower in the esmolol group; there was no difference in time for the first supplementation. Pain intensity was lower, except at T0 and after 12 h. There were no differences in side effects. Conclusions Intraoperative esmolol promotes an analgesic effect without causing adverse effects, making it an effective drug for multimodal analgesia for gastroplasty.

Introduction

In patients undergoing bariatric surgery postoperative recovery and analgesia are challenging.

Opioids are effective in relieving postoperative pain, however in obese these drugs are associated to complications, such as airway obstruction, increased time to anesthetic recovery, and the need for re-intubation [1].

Other drugs are often given in combination with opioids to increase their analgesic efficacy and decrease the incidence and severity of side effects. Also, lower half-life drugs are desirable in this group of patients [1].

Beta-adrenergic antagonists, such as esmolol, have been used in some studies for postoperative multimodal analgesia [2,3]. Several mechanisms have been proposed for the analgesic action of beta-blockers: modulation of calcium and potassium channels and adrenergic activity, inhibition of sodium channels and facilitation of inhibitory neurotransmitter release [2,4,5].

In several studies, there was a reduction in postoperative opioid consumption [2,6–8] and pain intensity [7,9]. However, in other study, esmolol failed to promote an analgesic effect [10].

The primary objective of this study was to evaluate the effect of esmolol infusion on analgesia after gastroplasty. The secondary objective was to assess the incidence of side effects.

The hypothesis of the study is that esmolol promotes a decrease in pain intensity and in the total opioid consumption.

Methods

The study was prospective, randomized, comparative, and double-blind. There were no changes in methods after the eligibility criteria.

The number of participants was calculated using the SPSS17® program. A difference of 3 in pain intensity was considered significant at 80% power and a 95% confidence interval. Based on a preliminary evaluation,[9] the estimated standard deviation of the pain intensity score within the groups was 2.2, and a sample size of 20 patients per group was calculated for a power of 0.95 and $\alpha = 0.05$.

Participants were randomly drawn and allocated to one of the groups. The randomization was performed by the Randomizer® program. The drawings for allocation in the groups were made by numbers placed in an envelope. On the day of surgery before the onset of anesthesia, the pharmacist opened the participant's envelope and prepared the solution according to the draw with esmolol or saline solution.

The anesthesiologist and the evaluator did not know which group the participant belonged to until the end of the study. In case of an emergency, the anesthesiologist caring for the patient could break protocol and see the group assignment.

After approval from the Ethics Committee (CAAE Nº 83115117.5.0000.5450) and signing the Consent Form, 40 patients aged 18–50 years, of both genders, physical status I or II by American Society of Anesthesiology (ASA), submitted to laparoscopic bypass gastroplasty were included in the stud. This study was conducted in accordance with the Declaration of Helsinki.

Patients with drug allergy; respiratory, renal, hepatic, cardiovascular or psychiatric disease; cognitive alteration; use of beta-adrenergic antagonists; or use of illicit drugs were excluded.

Monitoring was performed with a cardioscope, capnograph, pulse oximeter, noninvasive blood pressure, and neuromuscular blockade device.

Anesthesia was with fentanyl (5ug/kg), propofol (2–4mg/kg) and rocuronium (0.6mg/kg and as required), 50% oxygen (without nitrous oxide) and 2% sevoflurane. Remifentanil intraoperatively (0.05 to 0.2ug/kg/min) was given if the heart rate was greater than 15% and the systolic blood pressure was greater than 20% of the baseline values. The baseline heart rate and systolic blood pressure was defined as the mean of the two lowest measurements recorded during the 3- to 5-minute interval prior to anesthetic induction. In case of hypotension, defined as systolic blood pressure less than 80 mmHg or mean arterial pressure lower than 60 mmHg, a bolus of ephedrine (0.5mg IV) was administered; in case of bradycardia, defined as heart rate <50, a bolus of atropine was administered (0.5mg).

Before extubation, sugammadex (2 mg/kg) was administered; if necessary, an additional dose (2 mg/kg) was given. Patients were kept in the recovery unit and received oxygen (5 L/min), until saturation was greater than 92% in ambient air for 10 min. Side effects and complications were noted. Patients with heart rate < 45bpm or mean blood pressure <60 mmHg were withdrawn from the study and treated.

Participants were divided into two groups. Group 1 patients received a 0.5mg/kg bolus of esmolol in 30 mL of saline before induction of anesthesia, followed by infusion of 15 µg/kg/min until end of surgery; group 2 received a 30mL bolus of saline and infusion of the same volume as G1.

The study was retrospectively registered at Brazilian Clinical Trials Registry (ReBec–9w3k77). The data were collected at IGESP hospital, São Paulo, Brazil.

Postoperative pain was treated with venous morphine (5mg per dose) as required.

The following were evaluated: consumption of intra-operative remifentanil; time to supplementation; intensity of pain by numerical scale from 0 to 10 after extubation (T0) and 30 minutes,1h, 2h, 6h, 12h and 24h; morphine dose over 24h; and side effects

The primary outcome was pain intensity reduction. The secondary outcomes were need of analgesic complementation, and adverse effects. No change in outcome was made after the trial commenced.

The results were submitted to statistical analysis by SPSS® program. The following tests were used: Wilcoxon for age, weight, height, body mass index, duration of surgery, remifentanil, time to recovery, time to first supplementation, dose of morphine in 24h, and pain intensity; chi-square test for number of participants requiring remifentanil and morphine supplementation; and Fisher's test for side effects. The level of statistical significance was $p<0.05$.

Results

The CONSORT flowchart is shown in figure 1. There was no difference in demographic data, duration of surgery and ASA between the groups (table 1).

Intraoperative remifentanil supplementation was required in 3 patients in the esmolol group and in 17 in the saline group, and the dose was higher in the saline group. The time to wake up was shorter in the esmolol group. There was a need for supplementation with postoperative morphine in 17 patients from the esmolol group and 20 from the saline group; the morphine dose over 24 h was lower in the esmolol group. There was no difference in time to the first supplementation (table 2).

Pain intensity was lower over 24 h in the esmolol group, except at T0 and after 12 h (table 3).

There were no differences in side effects between groups (Table 4).

Discussion

Postoperative patient discharge requires efficient analgesia; absence of nausea, vomiting and ileus; and food intake. The drugs used in the postoperative period should promote early mobilization to avoid thromboembolism, as these patients already have difficulty moving.

Opioids promote analgesia but may cause side effects, especially in obese patients and at higher doses [11,12,13,14]. Drugs and obesity predispose patients to respiratory changes, with important implications in patients undergoing bariatric surgery. Thus, multimodal anesthesia with analgesics of different classes is the most prudent approach for morbidly obese patients. A combination of short-acting drugs with a focus on opioid reduction can reduce vomiting and pulmonary complications, enabling early ambulation and shortening the hospital stay [15].

No preanesthetic medication was given because benzodiazepines, especially midazolam, are related to the increasing respiratory complications in obese patients.[16]

Anesthesia was maintained with sevoflurane, which is rapidly eliminated from obese patients, with faster return of activities, less obstructive sleep apnea, and a low incidence of nausea and vomiting. Sevoflurane ensures hemodynamic stability and rapid recovery in morbidly obese patients [16,17,18].

Inadequate control of postoperative pain, nausea and vomiting are the most common causes of prolonged hospital stay.

In this study, analgesia was improved with esmolol, both during surgery and in the postoperative period over 24 hours, which can be considered a good effect of this drug. This result is similar to report in the literature focusing on other types of surgeries and patients with BMI within the normal range [6,8,20].

Remifentanil was used for intraoperative supplementation because although it is liposoluble, its degradation is rapid, and does not enter the lipophilic compartment. It is used safely in obese patients, with the volume of distribution and clearance being similar to that of the non-obese population [21].

Intraoperative esmolol may reduce the consumption of opioids and their side effects, such as nausea, vomiting and ileus, with less time to patient discharge.

In this study, a 0.5 mg/kg bolus was given, similar to the majority of literature reports [2,9,22]. Other authors administered 1mg/kg [23]. The infusion was performed at lower doses than those in the literature, which include reports of 5µg/kg/min [9], 10µg/kg/min [6], 30µg/kg/min [22], 50ug/kg/min [2,23], these previous studies were not conducted in the morbidly obese.

Esmolol was hemodynamically safe, and there were no differences in the incidence of bradycardia or hypotension between the groups, as in studies in the literature [6,8–10,22,24]. In this study, esmolol was not associated with significant bradycardia. Hypotension was related to boluses greater than 0.5mg in one review [24]. In one study in the esmolol group, the heart rate was slightly higher than that in the placebo group [9]. In another study, more bradycardia was observed with esmolol but with hemodynamic

stability [25]. Other studies have demonstrated hemodynamic benefits for orotracheal intubation [26] and reduced myocardial oxygen consumption by preventing adverse events during surgery [27].

There was no significant difference in the incidence of nausea and vomiting, unlike in previous studies [15,28,29], but nausea was less common in the esmolol group. However, a preventive antiemetic drug was administered in this study for both groups. There was one case of bronchospasm, but no correlation with esmolol, as it was observed in the saline group.

Conclusions

Intraoperative esmolol promotes an analgesic effect without significantly increased risks and represents an effective medicine for multimodal analgesia in obese patients subjected to gastroplasty.

Declarations

Acknowledgement:

to CAPES (Coordination of Improvement of Higher Education Personnel) - Finance Code 001.

Ethics approval:

Ethics Committee of Universidade Federal de São Paulo, CAAE Nº 83115117.5.0000.5450

Competing interests:

none

Consent to publish:

Consent Form

Availability of data and material:

at Universidade Federal de São Paulo, and Vinicius BD de Morais

Funding:

Institutional

Authors’ contributions:

(All authors have read and approved the article)

Acknowledgement:

to Coordination of Improvement of Higher Education Personnel (CAPES

Abbreviations

- VBDM: Article writing, data analysis and interpretation
- RKS: Study conception and design, article writing, critical revision of the intellectual content
- APSH: Study design
- LHCF: Data analysis

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Tables

Table 1. Characteristics of participants according to age, height, weight, body mass index, duration of surgery (mean± SD); gender and ASA physical status (number).

	Esmolol	Saline	P
Age (years)	35.8±10.9	33.2±8.7	0.379
Gender: M / F	3 / 17	3 / 17	NC
Weight (kg)	105.6±20.2	109.8±11.2	0.148:
Height (cm)	161.9±8.0	164.4±9.7	0.456
BMI (kg.m-2)	40.1±5.5	40.7±3.3	0.148:
ASA: I / II	0 / 20	0 / 20	NC
Duration of surgery	104.3±14.3	112.8±12.5	0.078

Wilcoxon test; BMI: body mass index; ASA: American Society of Anesthetists; NC: not calculated

Table 2. Intraoperative supplementation with remifentanil (dose and number of patients needing supplementation), time until recovery, time until first postoperative first supplementation, and morphine (dose in 24 h and number of patients needing supplementation) (mean ± SD).

	Esmolol	Saline	P
Intraoperative remifentanil (µg)	620.0±182.5	1058.8	0.001†:
Number who needed remifentanil	3	17	0.001‡
Time for recovery (min)	9.0 ± 3.4	12.5 ± 3.7	0.006†:
First supplementation (min)	247,5±514.2	33.0±19,2	0.145†:
Dose of morphine (mg)	7.0 ± 4.4	13.0 ± 5.7	0.002†:
Number who used morphine	17	20	0.100‡

†: Wilcoxon test; ‡: qui-square; SD: standard deviation

Table 3. Intensity of pain at recovery (T0), after 30 minutes, 1, 2, 6, 12 and 24 h, according to numerical scale – median (minimum- maximum)

	Esmolol	Saline	P
T0	0 (0 - 8)	0 (0 - 8)	0.180
30 min	5 (0 - 8)	6 (2 - 10)	0.032
1 h	5 (0 - 9)	8 (3 - 10)	0.004
2 h	2 (0 - 6)	5 (2 - 8)	0.002
6 h	3 (0 - 5)	4 (1 - 7)	0.047
12 h	1 (0 - 2)	1 (0 - 3)	0.262
24 h	0 (0 - 2)	1 (0 - 2)	0.029

Wilcoxon test; T0= at recovery of consciousness

Table 4. Side effects – number (%)

	Esmolol	Saline	P
Nausea	6 (30%)	9 (45%)	0.515
Vomiting	0 (0%)	0 (0%)	NC
Somnolence	9 (45%)	7 (35%)	1.000
Hypotension	3 (15%)	3 (15%)	1.000
Bradycardia	2 (10%)	2 (10%)	1.000
Bronchospasm	0 (0%)	1 (5%)	1.000

Fisher test; NC: not calculated

Supplementary Files

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- EsmololCONSORTFlowchartBMCAnesth.doc