Original Article

Effect of intravenous esmolol on analgesic requirements in laparoscopic cholecystectomy

Ritima Dhir, Mirley Rupinder Singh[1], Tej Kishan Kaul[1], Anurag Tewari[2], Ripul Oberoi

Departments of Anaesthesiology, Fortis Hospital, Gurgaon, [1]Dayanand Medical College and Hospital, Ludhiana, India, [2]Cincinnati Children's Hospital, Cincinnati, USA

Abstract

Background and Aims: Perioperative beta blockers are also being advocated for modulation of acute pain and reduction of intraoperative anesthetic requirements. This study evaluated the effect of perioperative use of esmolol, an ultra short acting beta blocker, on anesthesia and modulation of post operative pain in patients of laproscopic cholecystectomy.

Material and Methods: Sixty adult ASA I & II grade patients of either sex, scheduled for laparoscopic cholecystectomy under general anesthesia, were enrolled in the study. The patients were randomly allocated to one of the two groups E or C according to computer generated numbers. Group E- Patients who received loading dose of injection esmolol 0.5 mg/kg in 30 ml isotonic saline, before induction of anesthesia, followed by an IV infusion of esmolol 0.05 μg/kg/min till the completion of surgery and Group C- Patients who received 30 ml of isotonic saline as loading dose and continuous infusion of isotonic saline at the same rate as the esmolol group till the completion of surgery.

Results: The baseline MAP at 0 minute was almost similar in both the groups. At 8th minute (time of intubation), MAP increased significantly in group C as compared to group E and remained higher than group E till the end of procedure. Intraoperatively, 16.67% of patients in group C showed somatic signs as compared to none in group E. The difference was statistically significant. 73.33% of patients in group C required additional doses of Inj.Fentanyl as compared to 6.67% in group E.

Conclusions: We conclude that intravenous esmolol influences the analgesic requirements both intraoperatively as well as postoperatively by modulation of the sympathetic component of the pain i.e. heart rate and blood pressure.

Key words: Laparoscopic cholecystectomy, esmolol, intraoperative pain, beta blocker, postoperative pain

Introduction

Esmolol, an ultra-short acting beta blocker, has been demonstrated to modulate acute pain in chronically instrumented rats subjected to formalin test.[1] Though the exact mechanism is not known, Hageluken et al demonstrated that beta adrenergic antagonists activate G proteins in isolated cell membranes and suggesting that this property of beta blockers resemble the mechanism of central analgesia as induced by clonidine.[2] Previous studies have shown that continuous esmolol infusion decreased the plasma propofol concentration, and minimal alveolar anesthetic concentration (MAC) of isoflurane during propofol/nitrous oxide/morphine anesthesia.[3]

After a thorough literature search, studies assessing the role of esmolol in the modulation of pain and the associated cardiovascular changes in laparoscopic cholecystectomy were found lacking. Therefore, we hypothesized that perioperative beta-antagonist administration may be beneficial in reducing the intraoperative anesthetic and analgesic requirements.

Material and Methods

After approval by the hospital ethics committee and obtaining a written informed consent, a total of 60 adult patients of either sex, belonging to American Society of Anesthesiologists (ASA) Grade I and II, scheduled for laparoscopic cholecystectomy under general anesthesia, were enrolled in the study. The patients were randomly allocated

Address for correspondence: Dr. M Rupinder Singh
Department of Anaesthesiology, Dayanand Medical College and Hospital, Ludhiana, Punjab, India.
E-mail: drgurdeep@yahoo.com

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to one of the two Groups E or C according to computer generated random numbers.

Anesthesia Technician prepared the drugs in the infusion pumps (Baxter) and coded them. A uniform team of attending anesthesiologist/s recorded the observations and were blinded to the exact nature of the drug. Exclusion criteria included patients with cardiovascular, renal and respiratory co morbidities, allergies to opioids and test drug and dependence on opioids. Patients with history intake of analgesic drug like paracetamol, non steroidal anti-inflammatory drugs or opioid, were not included for the study.

Patients in Group E received a loading dose of injection esmolol 0.5 mg/kg in 30 ml isotonic saline, before induction of anesthesia, followed by an intravenous (IV) infusion of esmolol 0.05 mg/kg/min until the completion of surgery, whereas in Group C, patients received 30 ml of isotonic saline as loading dose and thereafter continuous infusion of isotonic saline at the same rate (0.05 mg/kg/min) until the conclusion of surgery.

After a thorough pre anesthetic checkup, all the patients were premedicated as per departmental protocol and fasting status ensured for at least 6 h prior to surgery. Monitoring of vital parameters such as heart rate (HR), noninvasive blood pressure (NIBP), respiratory rate (RR), pulse oximetry (SpO_2) and electrocardiography (ECG) was initiated. A patent 18G IV access was achieved in left arm.

Prior to induction, patients received fentanyl 1.5 μg/kg intravenously after preoxygenation with 100% oxygen for 3 min, anesthesia was induced with IV propofol 1-2 mg/kg. Tracheal intubation was facilitated by injection rocuronium intravenously. Anesthesia was maintained using controlled ventilation with isoflurane 0.5-1.0% and O_2:N_2O in the ratio of 30:60. Neuromuscular blockade was achieved with atracurium 0.5 mg/kg IV. Vital parameters including HR, NIBP — systolic, diastolic and mean, end tidal carbon dioxide ($EtCO_2$), SpO_2 and ECG were monitored throughout the procedure.

The following parameters, increase in HR >20% above baseline for >1 min, increase in mean arterial pressure (MAP) >20% above baseline for >1 min and presence of somatic signs (like purposeful movements, swallowing, grimacing) or autonomic signs (lacrimation, sweating, facial flushing) were assessed by the attending anesthesiologist and considered as signs for inadequate anesthesia and analgesia and appropriately treated. In the presence of two or more than two parameters, depth of anesthesia was increased by increasing the concentration of isoflurane by 0.2%, and analgesia was supplemented with injection fentanyl in the boluses of 10-20 μg till the hemodynamic profiles returned to the baseline values. Any episode of bradycardia, that is, HR <50-beats/min and hypotension, that is, MAP <90 mmHg was managed with IV atropine 0.01 mg/kg and ephedrine 0.05 mg/kg respectively.

The duration of surgery was recorded in all cases. At the completion of surgery, patients had their infusion discontinued. Residual neuromuscular blockade was reversed with neostigmine 2.5 mg and glycopyrrolate 0.5 mg intravenously. After extubation, patients were shifted to post anesthesia recovery care unit wherein HR, NIBP, RR and SpO_2 were recorded every 5 min for the first half an hour, and then half hourly till 4th h and then every 4 h till completion of 24 h. Visual analogue scale ≥3 was treated with a supplemental dose of tramadol 50 mg intravenously. Total amount of rescue analgesics required and the trend of VAS scores in postoperative period were also recorded.

After completion of the study, observations obtained were tabulated and analyzed using Student's *t*-test, Chi-square test and *z*-test. Sex differences were tested for significance by applying Chi-square test. $P < 0.05$ was considered as significant.

Results

The demographic profile (mean age, weight and sex) of the patients was comparable in both the groups [Table 1].

Intra-operative hemodynamic parameters

The baseline mean HR, MAP, mean systolic and diastolic blood pressure, were similar in both groups and statistically comparable from 0 min to 8 min. The hemodynamic parameters in Group C significantly increased from 8th min onwards (approximately coinciding with the time of intubation) and remained higher till end of the procedure [Figures 1 and 2]. Only 10% of patients in Group E

Table 1: Demographic profile

Parameter	Group E	Group C	*t* value	*P* value	Chi-square
Mean age±SD	45.33±13.78	51.23±13.64	1.67	0.09	
Gender: Male/female	4/26	5/25		0.75	0.13
Mean weight±SD	67.70±13.07	66.23±10.14	0.49	0.34	

SD = Standard deviation

showed statistically significant ($P = 0.004$) increase in intra-operative HR as compared with 86.67% in Group C. Similarly, statistically significant increase in MAP was observed in 80% patients of Group C when compared to 6.67% in Group E.

Intra-operative somatic and autonomic signs

Statistical significance ($P = 0.04$) was noted when 5 (16.67%) patients in Group C exhibited somatic signs when compared to none in Group E. Similarly seven (23.3%) patients of Group C demonstrated autonomic signs in contrast to 1 (3.33%) in Group E (statistically significant $P = 0.04$).

Intra-operative rescue analgesic and isoflurane requirements

Twenty-two (73.33%) patients in Group C required additional doses of Fentanyl as compared to 2 (6.67%) in Group E (statistically significant $P = 0.005$). Fifteen (50%) patients in Group C required an increase in concentration of isoflurane as compared to 6.67% in Group E (statistically significant $P = 0.007$).

Postoperative monitoring

Trends in visual analogue scale

At 0 h the mean pain score was elevated and statistically significant ($P < 0.001$) in Group C as compared to Group E. The highest mean pain score in Group C was 4.77 + 1.81 at 0 h followed by 4.00 ± 1.84 at 3rd h. The highest mean pain score in Group E was 3.47 + 1.66 at 12th h postoperatively. Mean pain score was higher in Group C when compared with Group E, at all-time intervals [Figure 3].

Postoperative rescue analgesic requirements

In Group C, 4 (13.33%) patients required first rescue analgesic at the 2nd postoperative h, 21 (70%) patients needed it at the 3rd, and 5 (16.67%) patients demanded in the 4th postoperative h. None of the patients in Group E, required first rescue analgesic till the 4th postoperative h. Only 1 (3.33%) of the patients was given first rescue analgesic at the 4th h, 9 (30%) at 8th h and 17 (56.67%) of patients were given first rescue analgesic at the 12th postoperative h. Significantly more number of patients had analgesic requirement at 3rd postoperative h in Group C, ($P < 0.001$) as compared to the 12th h in Group E ($P = 0.008$).

Postoperative hemodynamic trends

As shown in Figure 4, postoperative mean HR was significantly higher in Group C as compared to Group E except at the 12th h ($P = 0.66$). The mean systolic blood pressure was significantly higher in Group C as compared to Group E except at 12th ($P = 0.16$) and 16th h ($P = 0.17$). The mean diastolic blood pressure was significantly higher statistically in Group C as compared to Group E for most of the times [Figure 5]. Both groups were comparable with regard to SpO_2 values.

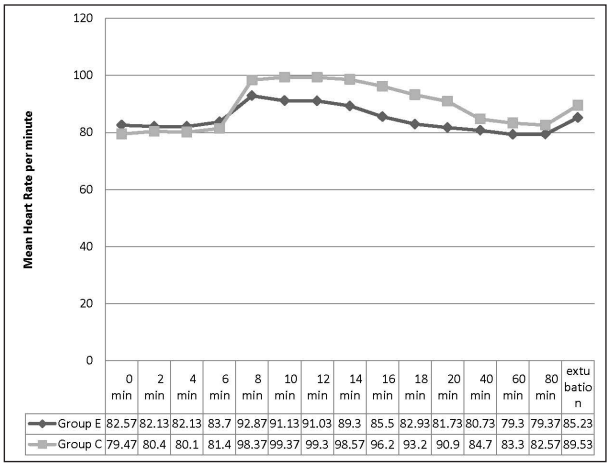

Figure 1: Intra-operative trends in heart rate among subjects in the two groups

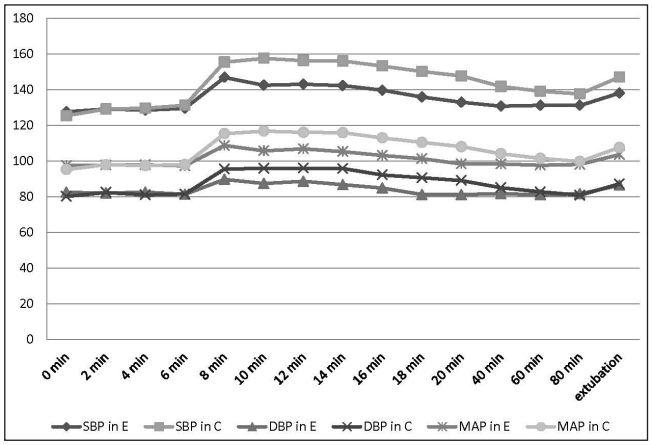

Figure 2: Intra-operative hemodynamics in both groups

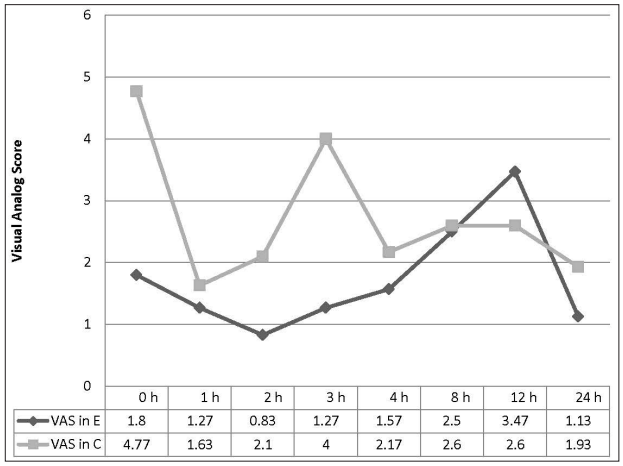

Figure 3: Trends in visual analog scale among subjects in the two groups

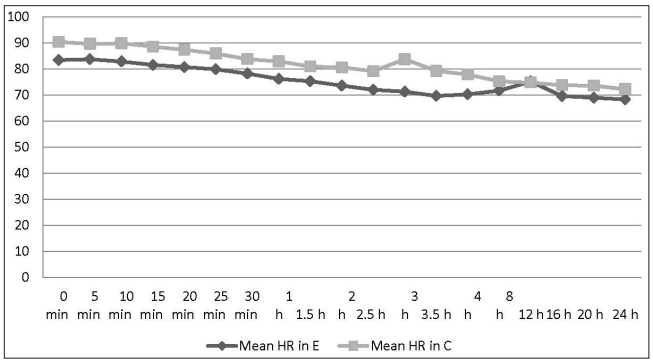

Figure 4: Postoperative trends in heart rate among subjects in the groups

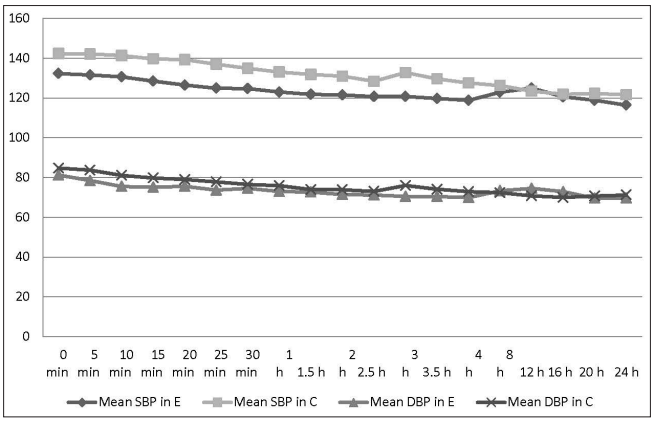

Figure 5: Postoperative hemodynamics in both groups

Discussion

The results of our study exhibit significantly decreased isoflurane and fentanyl requirements alongwith a lesser degree of variation in hemodynamics, fewer autonomic and somatic signs intraoperatively in group E as compared to group C. This trend of stable hemodynamics and reduced analgesic requirements continued in group E into the postoperative period thereby suggesting role of esmolol in modulating postoperative pain.

Although the role played by esmolol in the modulation of postoperative pain remains to be established, yet a few studies have thrown light on the mechanism behind the analgesic effects of esmolol. Beta adrenergic antagonists activate G proteins in isolated cell membranes. This property of beta blockers resembles the mechanism of central analgesia as induced by clonidine.[2] Inhibitory G protein coupled receptor agonists act upon post synaptic inhibition via G protein coupled potassium channels or via the presynaptic inhibition of neurotransmitter release through the regulation of voltage gated calcium ion channels. Such a pathway underlies the antinociceptive effects of clonidine.[4]

Esmolol has been postulated to reduce anesthetic requirements via a direct antinociceptive property. Use of esmolol and nicardipine in patients undergoing gynecological laparoscopic procedures attenuated the increase in HR and MAP intra-operatively, facilitated faster emergence from anesthesia and significantly decreased postoperative analgesic requirements and time to discharge, without increasing any side effects.[5]

Chia *et al.* studied the effect of IV esmolol on intra-operative and postoperative analgesic requirements after total abdominal hysterectomy. The patients in the esmolol group (received IV loading dose of 0.5 mg/kg/min followed by an infusion of 0.05 μg/kg/min) showed significant less patient-controlled analgesia (PCA) morphine consumption over 3 days postoperatively in comparison to the control group (received similar volumes of normal saline) who used greater quantities of PCA morphine at all times in the study.[6]. Similar results in regard to reduced analgesic requirements were observed in our study. Pain is a stressful condition, which stimulates sympathetic responses in the human body.[7] The hemodynamic parameters postoperatively could be a measure of the pain status of the patient.[8] In our study, upto 24 h postoperatively, the control group showed significantly higher mean HR, diastolic and systolic blood pressures when compared to the esmolol group at all-time intervals except for at 12th h when mean HR and systolic blood pressures were almost same in both the groups. This could be explained by the fact that at 12th h, maximum patients in the esmolol group experienced significant pain for the 1st time after 0 h. Furthermore, beta-1-selectivity of esmolol is associated with lower HR.[9]

Zaugg et al found that administration of beta antagonist did not influence the pro-inflammatory or inflammatory interleukin profiles. This suggests that the beneficial impact of beta antagonist on anesthesia and postoperative pain management is not necessarily attributable to suppression effect of stress hormones or pro inflammatory cytokines.[10]

In a study the effect of beta blockade with norepinephrine and various other adrenergic antagonists on spontaneous gamma-aminobutyric acid (GABA) receptor mediated postsynaptic currents of the on-cells from the periaqueductal gray region in the midbrain has been evaluated. These cells mediate pain transmission and are under the control of GABAergic neurons. An increase in GABA release interrupts pain transmission. The results of this study suggested that the activation of α_1 and β_2 receptors increased GABA release whereas activation of β_1 receptors suppressed GABA release.[11] These results suggested that increasing GABA levels in the brain by selective blockade of β_1 receptors may constitute a new and useful target for prospective pharmacotherapeutic approaches in the management of acute and chronic pain.

Conclusion

Hence, we conclude that the intraoperative use of esmolol attenuated nociceptive stimulation as evidenced by reduced intraoperative anesthetic and analgesic requirements, hemodynamic variations and fewer autonomic and somatic signs. The use of esmolol also contributed to decreased post operative analgesic requirements possibly by modulation of the sympathetic component of the pain. Further studies on esmolol exploring its potential in modulating the pain pathways are warranted.

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Conference Calendar 2015

Name of conference	Dates	Venue	Name of organising secretary with contact details
19th Annual National Conference of IACTA IACTA 2016	February, 12-14th, 2016	Radisson BLU Resort Temple Bay, Mamallapuram Chennai	Dr Mahesh Vakamudi Organising Secretary IACTACON - 2016 A6 OR Complex, Department of Cardiac Anesthesia. Sri Ramachandra University. No 1, Ramachandra nagar, Porur, Chennai - 600116 Phone: +91 44 23860125 Mobile: +91 90426 06596
23rd International Conference of the Indian Association of Palliative Care IAPCON 2016	February, 12-14th, 2016	Pune	Dr. Priyadarshini Kulkarni Telephone: 919158286161 Email Id: info@iapcon2016pune.com Website: http://iapcon2016pune.in/index.html