

EFFECT OF INTRAOPERATIVE ESMOLOL INFUSION ON POSTOPERATIVE ANALGESIA IN LAPAROSCOPIC CHOLECYSTECTOMY PATIENTS: A RANDOMISED CONTROLLED TRIALShreya Lahiri¹, Sabyasachi Das², Sekhar Ranjan Basu³**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: BACKGROUND: Laparoscopic cholecystectomy, gaining worldwide popularity, can be performed on a short stay basis if postoperative pain is adequately addressed. Our present study determines the effect of intraoperative infusion of intravenous esmolol primarily in terms of postoperative analgesia and intraoperative haemodynamic stability. **METHODS:** 60 ASAPS 1 and 2 patients undergoing elective laparoscopic cholecystectomy were included in this randomised, prospective, placebo-controlled clinical study. Patients were allocated into two groups to receive intraoperative intravenous esmolol (Group A, n=30) or normal saline (Group B, n=30) over a period of 10 minutes before induction. Intraoperative heart rate, mean arterial pressure and postoperative fentanyl requirement (During first 6 postoperative hours) were recorded. **RESULTS:** Postoperative requirement of fentanyl was significantly lower (92.73 ± 17.42 mcg in group A compared to 117.32 ± 19.22 mcg in group B, p value <0.01) in patients of esmolol group. Intraoperative heart rate and MAP were better maintained in patients receiving esmolol, however, it failed to achieve any statistical significance (p>0.05). **CONCLUSION:** Intravenous esmolol effectively reduces postoperative fentanyl requirement, thereby is a safe adjunct in the field of postoperative analgesia for laparoscopic cholecystectomy.

KEYWORDS: Esmolol, laparoscopic cholecystectomy, postoperative analgesia, intravenous infusion.

INTRODUCTION: Laparoscopic cholecystectomy (LC) has gained worldwide popularity as a short-stay basis procedure.¹ Although, acute postoperative pain after laparoscopic cholecystectomy can lead to a significant morbidity and slow patient recovery. This pain is considered unique as its characteristics are not limited to incisional and visceral deep pain, but also encompasses referred shoulder pain. Perioperative analgesia has traditionally been provided by systemically administered opioids. However, their extensive use is associated with a spectrum of perioperative side effects that can delay hospital discharge.² Therefore, surgical patients would greatly benefit from a perioperative analgesic regimen, alternative or supplementary to systemic opioids. A prophylactic multimodal analgesia regimen had been tried to reduce postoperative pain in laparoscopic cholecystectomy patients.³ In spite of this multiparmacological intervention, postoperative analgesia has not been consistently satisfactory.⁴ So, search for adjuvant therapies to reduce doses of opioids, continues.

Studies in the last decade have shown that β adrenergic receptor antagonists suppress surgery induced increase in circulating catecholamines and possess anaesthetic and analgesic sparing effects.⁵ Esmolol, an ultrashort acting β_1 blocking agent has been found to possess opioid sparing properties probably due to structural similarities with local anaesthetics. The desirable property of esmolol is its titrability and short duration of action. However, its mechanism of action as an analgesic has not yet been established and comprehensive evidence of its analgesic effect is not

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available. To measure the opioid sparing effect of esmolol on laparoscopic cholecystectomy patients, this study was carried out in the Department of Anaesthesiology, North Bengal Medical College and Hospital. Primary outcome of this study being the amount of fentanyl required during first six postoperative hours to maintain VAS score ≤ 3 at rest or ≤ 4 upon movement.

MATERIALS AND METHOD: After obtaining the institutional ethics committee approval, this randomised, double-blinded, placebo-controlled trial was carried out between January and December 2010 in the department of General Surgery & Anaesthesiology of North Bengal Medical College and Hospital.

During the pre-anaesthetic checkup, written informed consents (After proper explanation of the study procedure in their own languages) were obtained from all the participants. Patients were explained before surgery in the use of VAS (Visual analogue scale) score (0 to 10) to assess postoperative pain.

On arrival of the patient in the operation theatre, baseline values of heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), peripheral arterial oxygen saturation (SpO₂) and temperature were recorded. Patients were preloaded with Ringer's lactate solution (10ml/kg).

The study drug was prepared before induction by a junior resident who did not take part in further data retrieval or analysis. Ten ml of inj. esmolol (100mg) was diluted with 40ml of normal saline to make a 2mg/ml esmolol solution. The anaesthesiologist in charge of the case was unaware of the patient's group assignment undertook the anaesthetic procedure, another anaesthesiologist performed the assessments and intraoperative data retrieval.

Before induction of anaesthesia, all the patients of either Group A or Group B received intravenous inj fentanyl (2mcg/kg). Patients in the esmolol group received the bolus dose 0.5mg/kg over 10min followed by continuous infusion of esmolol (10-20mcg/kg/min) via an infusion pump till extubation so as to maintain heart rate within 20% of baseline. Patients in group B received same volume of normal saline at the same rate.

General anaesthesia was induced with propofol (2-2.5mg/kg) until the loss of verbal contact. Optimum intubating condition was achieved by using muscle relaxant vecuronium (0.1mg/kg) and intubation was done under direct laryngoscopy after 90seconds. Adequate plane of anaesthesia was maintained with N₂O in O₂, isoflurane (0.2-0.8%) to maintain the heart rate and systolic blood pressure within $\pm 20\%$ of respective baseline values. Supplemental neuromuscular blockade was achieved with vecuronium at 20 minutes interval.

Intraoperative minute ventilation was continued so as to maintain normocarbica (EtCO₂ between 35- 40mm/Hg). Intraabdominal pressure was maintained below 12mm Hg. No local anaesthetic infiltration was done.

Episodes of intraoperative hypotension (MAP<60mm Hg) was treated with intravenous boluses of phenylephrine and bradycardia (HR<50/min) with atropine. There was a definitive back up plan provided to the attending anaesthesiologist to address intraoperative haemodynamic instability and awareness.

Isoflurane was discontinued after the last skin suture and on return of flickering movement on the reservoir bag, N₂O inhalation was stopped. Reversal of residual neuromuscular blockade was achieved with incremental dosing of intravenous inj. neostigmine (up-to a maximum of 0.07mg/kg) and glycopyrrolate (0.01-0.02mg/kg). Tracheal extubation was done when standard criteria of

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extubation were fulfilled. Inj. diclofenac (1mg/kg) was administered as infusion over 15minutes, 10-15 min before extubation in both the groups to achieve optimum analgesia.

All the operative procedures were performed by two surgeons who were highly experienced in performing laparoscopic cholecystectomy.

After adequate reversal, all the patients were transferred to the post anaesthesia care unit (PACU) for assessment during next 6hours. During this period, VAS score (Pain assessment), HR, SBP, DBP, ECG, SpO₂ were monitored by a junior resident unaware of the intraoperative anaesthesia record. No intraoperative data were available in the PACU.

At the PACU, during first 6 post-operative hours, inj. fentanyl was prescribed for postoperative pain relief as 10mcg aliquots on demand so as to maintain VAS score ≤ 3 at rest or ≤ 4 with movement. Maximum allowable dose was 100 mcg of inj. fentanyl over 1hr. VAS scores were noted at 10 min interval during first 30 min, thereafter hourly for next 6 hours.

Total iv fentanyl requirement in the PACU (During first 6 post-op hours) was noted. Incidence of any adverse event like PONV, sedation, headache was also noted.

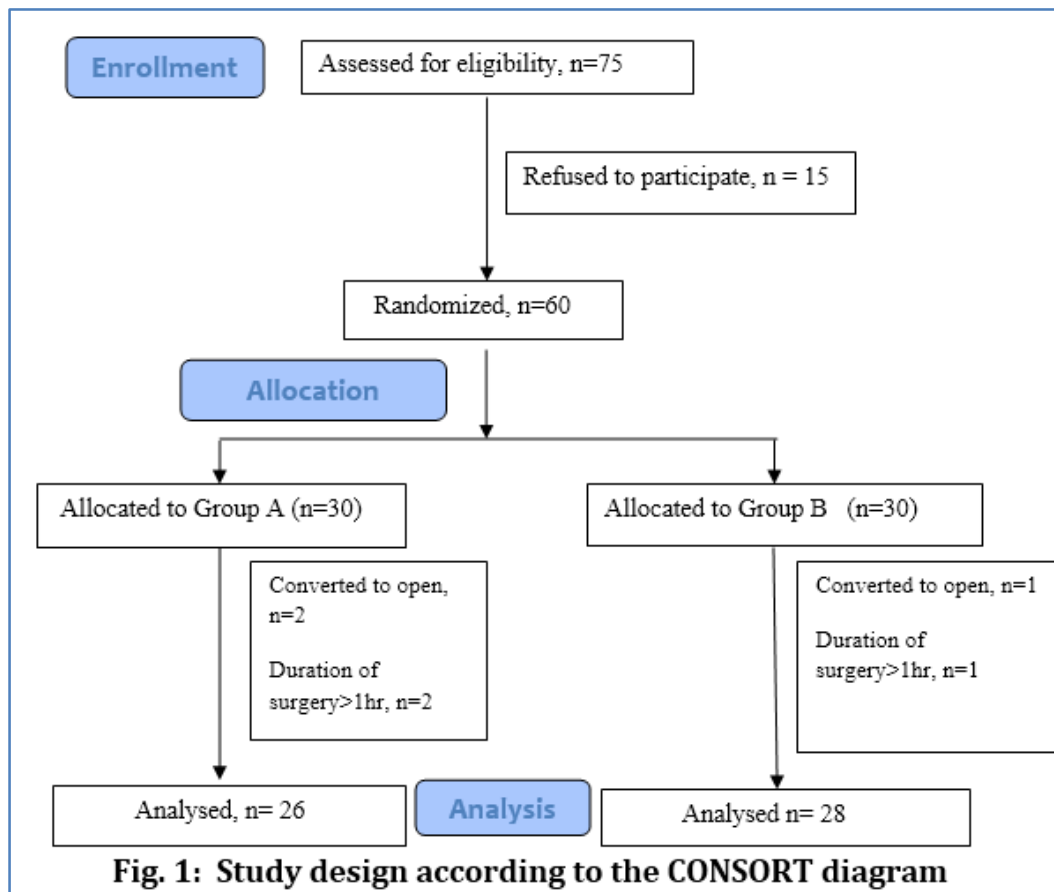
RESULTS: We started our study with 60 patients (Sample size was found to be 50), who were randomized according to a computer generated random number table and assigned to receive either esmolol, the study drug (Group A, n=30) or normal saline (Group B, n=30). The surgical procedure of two patients of Group A and one patient of Group B were converted from laparoscopic to open cholecystectomy resulting in exclusion of those patients. Another two patients of Group A and one patient of Group B were excluded from our study as their procedure lasted for more than one hour. Therefore data of remaining 54 patients were assessed for final analysis (Group A=26, Group B=28). The details of the conduct of the study are shown in Figure 1.

Patients' demographic parameters and surgical factors were not different between two groups (Table 1). Patients in the esmolol group required significantly lower amount of fentanyl compared to group B patients during 1st six postoperative hours to maintain VAS score ≤ 3 at rest or ≤ 4 upon movement. Group A patients required 92.73 ± 17.42 mcg of fentanyl, while group B patients required 117.32 ± 19.22 mcg. ($p < 0.001$). (Table 2). Time to first requirement of analgesic in the immediate post-operative period in group B was significantly earlier as compared to group A. Group B patients required the first dose of analgesic at 21.11 ± 7.192 min while group A patients required at 28.85 ± 7.598 min. ($p < 0.001$). (Fig 2)

Comparison was done between the two groups in terms of heart rate and mean blood pressure at various time points. There was a decline in heart rate from the baseline value in group A after administration of the bolus dose which is statistically significant compared with group B ($p < 0.05$). Throughout the operative period the mean values of heart rate in group A were significantly lower than that of group B ($p < 0.05$), however, the mean values of heart rates in the postoperative period in both groups were comparable ($p > 0.05$); (Fig 3). Only one patient of group B had an episode of intraoperative bradycardia whereas two patients of group A encountered such single episode. Though group A seems to have more incidence of intra operative bradycardia, statistical analysis (Pearson Chi-square test) revealed no significance ($p = 0.454$) compared to group B. ($p > 0.05$).

The mean VAS scores in group A patients were lower than group B patients postoperatively, but failed to achieve any statistical significance (p value > 0.05). Reduced incidence of PONV and ondansetron requirement in Group A during immediate postoperative period and first postoperative hour were noted.

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| Demographic data | GROUP A (n=26) | GROUP B (n=28) | P VALUE | 95% Confidence interval | |
|---------------------------|----------------|----------------|---------|-------------------------|-------|
| | | | | Lower | Upper |
| Age (years) | 36.81±3.533 | 37.64±3.413 | 0.382 | -2.735 | 1.065 |
| Height (cm) | 158.77±6.153 | 159.32±6.056 | 0.741 | -3.890 | 2.786 |
| Weight (kg) | 60.5±4.632 | 62.5± 4.796 | 0.125 | -4.575 | 0.575 |
| BMI (kg/m ²) | 24.01±1.466 | 24.62±1.353 | 0.116 | -1.387 | 0.158 |
| Sex (M/F)# | 11/15 | 12/16 | 0.967 | | |
| ASA (1/2)# | 22/4 | 23/5 | 0.808 | | |
| Baseline heart rate | 78.85±6.839 | 80.54±6.015 | 0.341 | -5.221 | 1.842 |
| Baseline MAP (mm of Hg) | 90.96±4.275 | 91.36±5.042 | 0.757 | -2.943 | 2.152 |
| Duration of surgery (min) | 45.62±5.886 | 46.29±5.603 | 0.671 | -3.815 | 2.474 |

Table 1: Demographic parameters and duration of surgery

Data expressed as mean ± SD.

Data expressed in numbers.

Tests done: Independent samples t test,
(p< 0.05 considered significant).

Pearson Chi-square test.

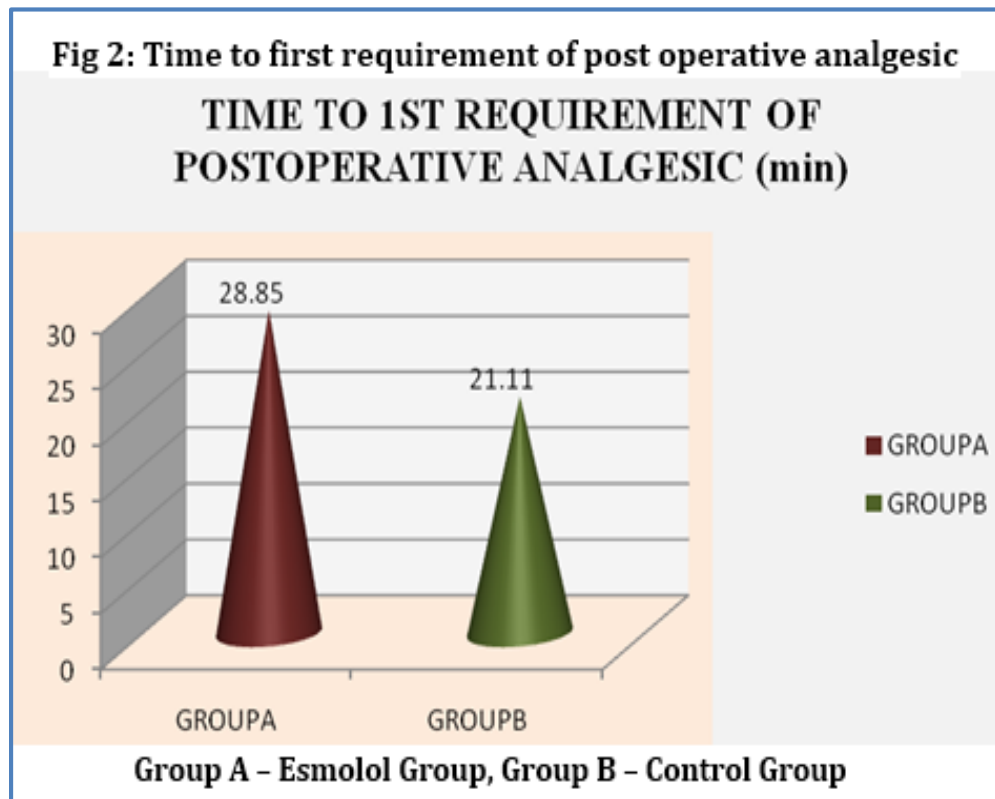
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| | Group A (n=26) | Group B (n=28) | P value | 95% Confidence interval | |
|---------------------------------|-------------------|-------------------|---------|-------------------------|---------|
| | | | | Lower | Upper |
| Total fentanyl consumption(mcg) | 92.73±17.421 | 117.32±19.22 | 0.000* | -34.597 | -14.584 |

Table 2: Total fentanyl consumption (mcg) during 1st six post-operative hours

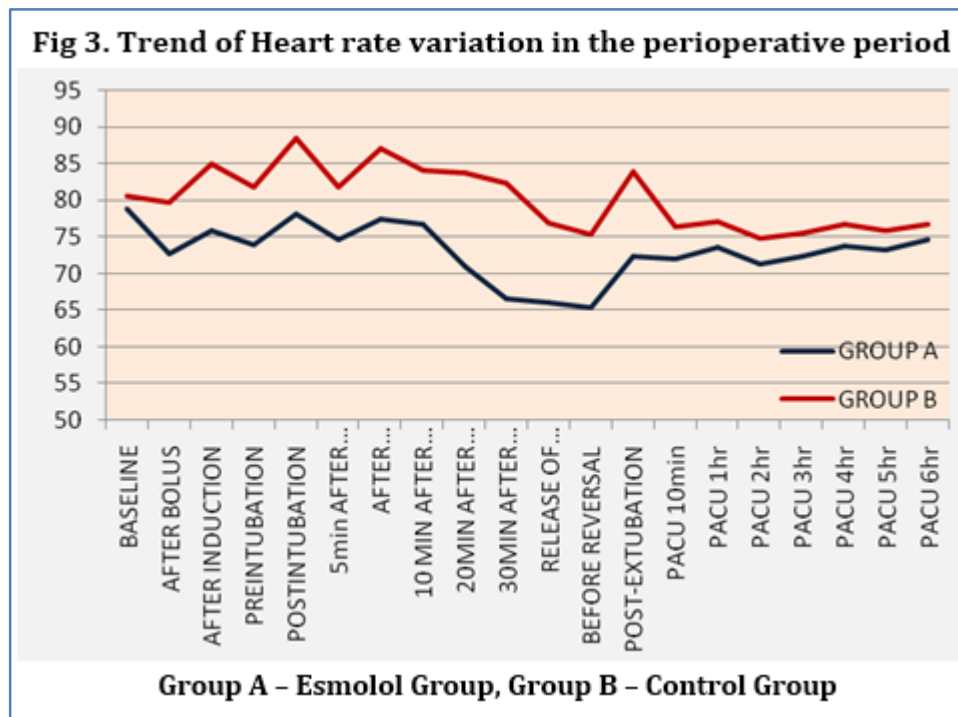
Data expressed as mean ± SD. Test done: Independent samples t test.
(* p < 0.05 considered significant).

Fig. 2: Bar diagram showing time to first requirement of postoperative fentanyl (represented along Y-axis) among Group A and Group B patients.



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Fig. 3: Line diagram representing trend of perioperative heart rate. Heart rate (beats per minute) is shown along Y-axis and time along X-axis.



DISCUSSION: Postoperative pain management is not only a surgeon's concern but also the moral responsibility of an anaesthesiologist. Laparoscopic cholecystectomy, one of the most extensive surgeries performed on a short stay basis, is the most common surgery performed laparoscopically and has almost replaced open cholecystectomy. As the pain characteristic of laparoscopic cholecystectomy is unique in nature, optimum analgesic intervention is still being searched.

Esmolol, an ultrashort acting β blocker having the advantage of titrability is ideal for use in the perioperative settings. Safety, efficacy and titrability of intraoperative esmolol infusion had been established in a recent meta-analysis.⁶ The present study claims about 21% reduction in fentanyl consumption during first six post-operative hours to maintain VAS ≤ 3 at rest or ≤ 4 upon movement. Group A patients required a mean dose of 92.73(SD 17.421) mcg of fentanyl whereas group B patient consumed 117.32(SD 19.22) mcg during first six post-operative hours ($p < 0.001$, table 2). Collard V and associates noted similar pattern of analgesic consumption (45% reduction in fentanyl dose) in the post-operative period using intraoperative esmolol infusion in patients undergoing laparoscopic cholecystectomy.⁷ Chia YY and co-workers observed 25% reduction of morphine consumption of patient controlled analgesia (PCA) in patients undergoing hysterectomy.⁸ Different methodology and study design might have been responsible for the variation in results of our study from others'. However, in another study Koivusalo AM, et al. demonstrated no change in the need for analgesics during the post-operative period using intra operative esmolol.⁹ The mechanism responsible for the analgesic like effect of esmolol is still an open question. There is evidence to suggest that significant effect of β blocker exists on the central nervous system. Esmolol was found to possess analgesic like properties in a rodent model by Davidson and colleagues.⁵ Local anaesthetic like property was also

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demonstrated. Another possible mechanism for the reduced fentanyl consumption in the post-operative period is the decreased hepatic blood flow caused by esmolol. This results in slower metabolism of opioid and prolongation of their analgesic effect, reducing the need of post-operative analgesic use.

There are lot of disagreements in literature to use bolus or infusion of esmolol. Bolus method is the one most commonly practiced for its convenience. In their meta-analysis, Yu SKH and coauthors found the bolus dose of esmolol varying between 1 and 4 mg/kg.⁶ Combination of a bolus dose and infusion was evaluated in several trials with initial bolus dose ranged from 0.3mg/kg to 2.3 mg/kg. The median bolus dose before the initiation of an infusion was 500mcg/kg, whereas bolus studies used an initial dose of >1mg/kg. To clear the confusion between bolus and esmolol infusion Figueredo, et al. opined that a better option is bolus followed by continuous infusion started before induction of anaesthesia to achieve constant plasma level of esmolol.¹⁰

In the present study, esmolol was infused at a flexible dose range of 10-20mcg/kg/min keeping the heart rate and MAP within 20% from the baseline value. In group A, two episodes of bradycardia requiring treatment and one episode of hypotension requiring treatment were noted. Whereas in group B only one patient required intervention for bradycardia and no episode of hypotension was noted. Though more episodes of bradycardia were encountered in Group A patients receiving esmolol, this observation could not achieve statistical significance.

However, fixed infusion rate of esmolol used in some studies was associated with unanticipated hypotension and bradycardia. The finding of a dose-response relationship between esmolol and hypotension has been previously demonstrated.¹⁰ The haemodynamic effects of esmolol are thought to be mediated by blockade at peripheral β -adrenergic receptors.

In the current study esmolol was infused till extubation and analgesic consumption and vital parameters were observed during first six post-operative hours.

Injection diclofenac was administered as pre-emptive analgesic. Studies suggested initiation of NSAIDs shortly before or during laparoscopic cholecystectomy to have optimum effect.¹¹ However in a few studies, no pre-emptive analgesic was administered. Collard V, et al. administered only esmolol without co administration of any analgesic during surgery.⁷

Reduced incidence of PONV and lesser ondansetron requirement in group A during immediate postoperative period and first postoperative hour were noted. This result could not reach statistical significance ($p>0.05$). However PONV at sixth hour was significantly less in group A ($p=0.024$). Our result corroborated with the findings of Ozturk T and colleagues.¹² They found PONV to be less severe in esmolol group ($p<0.001$). Coloma M, et al. found that esmolol decreased the incidence of PONV compared to remifentanyl (4% and 35%) for outpatient gynaecological surgeries using desflurane and remifentanyl.¹³ However, Smith and colleagues found that esmolol, when compared with alfentanil as a supplement to propofol-nitrous oxide anaesthesia, did not decrease the incidence of PONV in patients undergoing arthroscopic procedures.¹⁴ Although there is no definitely agreed upon theory, intraoperative esmolol use reduced the required dosage of postoperative fentanyl, which might have decreased the likelihood of opioid related side effects like PONV.^{12,13} We cannot conclude anything regarding PONV from our study as it was not designed to comment on secondary outcomes like PONV.

One of the most important limitations of our study was not monitoring BIS in all cases. As depth of anaesthesia was maintained according to haemodynamic parameters, a possibility of awareness and light plane remained with the administration of esmolol. The use of a BIS monitor

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would have ensured that both the groups had similar depth of anaesthesia. We have administered preemptive diclofenac in all the patients. As our primary outcome was measurement of postoperative pain using esmolol, diclofenac could have been a confounding variable. We could not measure the plasma concentration of esmolol. If measured, it might have corrected the possibility of inter-individual variability, so also help to comment on optimum analgesic plasma concentration of esmolol. Pain being a subjective phenomenon, should be individualised for better management.

In future, further studies can be carried out to assess the beneficial effects of esmolol in more extensive and painful surgeries. The optimum dosage, timing and duration of esmolol infusion can be studied.

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