

The Effect of Intravenous Esmolol on Requirement of Desflurane and Post Operative Pain in Laparoscopic Cholecystectomy

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Abstract: Background: The use of β -blockers for hemodynamic stability and cardiac protection is well accepted among anaesthesia providers, but recently, researchers have begun to explore the perioperative use of Esmolol as an anaesthetic adjunct. Thus our present study was aimed to observe the effect of intravenous Esmolol on the requirement of Desflurane and analgesic agent for postoperative pain along with its effect on hemodynamic parameters. Method: ASA grade I & II patients ($n=188$), scheduled for laparoscopic cholecystectomy under general anesthesia, were enrolled for the study. The patients were randomly allocated to one of the two groups A or B according to chit and box method. Group A- Patients received loading dose of injection Esmolol 0.5 mg/kg in 30 ml isotonic saline, 20 min before induction of anesthesia over a period of 5 minutes, followed by an IV infusion of Esmolol 0.05 mg/kg/min till the completion of surgery and Group B- Patients 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 two groups were comparable with respect to Demographic data. Total consumption of Desflurane was significantly less in group A. Assessment of postoperative pain by Visual Analogue Scale up to 24 hrs showed significant difference in two groups and total dose of analgesic required for pain relief was significantly less ($P<0.05$) in Group A. Conclusion: Esmolol reduces requirement of desflurane intraoperatively, decreases postoperative pain, and analgesic requirement. Esmolol also stabilizes hemodynamic parameters.

Keywords: Esmolol, Desflurane, laparoscopic cholecystectomy

1. Introduction

Esmolol is an ultra-short acting beta-blocker widely used in anaesthesia practice to blunt adrenergic response to laryngoscopy, endotracheal intubation and extubation. Esmolol minimizes the deleterious effects of intraoperative hypertension and tachycardia on myocardial oxygen consumption¹⁻³. The use of β -blockade for hemodynamic stability and cardiac protection is also well accepted. Research also suggests that the use of esmolol results in decreased postoperative nausea and vomiting, earlier discharge, and increased patient satisfaction⁴. Recent research focus on perioperative use of esmolol as an adjunct to reduce the anaesthetic and analgesic requirement. This opioid sparing effect is still underused in clinical settings. Thus our study was aimed to observe the effect of beta blocking agent, Esmolol on requirement of Desflurane intraoperatively, post operative pain and analgesic requirement in laparoscopic cholecystectomy.

2. Material and Method

This hospital based prospective randomized comparative interventional double blind study was conducted at SMS medical college and attached group of hospitals from November 2017 to February 2018, after permission from Research Review Board and ethics committee. After taking written informed consent, 188 ASA grade I and II patients of either sex, undergoing laparoscopic cholecystectomy were included in our study. Patients with history of allergy to opioids or halogenated anaesthetics, or taking drugs and/or medications known to influence anaesthetic requirement including beta-blockers and opioids, pregnant patients and patients with clinically significant cardiovascular, pulmonary, renal, and hepatic diseases were excluded from the study. Patients were randomly allocated into two groups using chit and box method.

On the day of surgery, patients were taken in OT. Written, informed consent and PAC was checked. Fasting status of 6 hours was confirmed. Standard monitors for (HR, SBP, DBP, MAP, SpO₂ and ECG) were attached.

The patients were premedicated with inj. ranitidine (1mg/kg), inj. Metoclopramide (0.15mg/kg), inj. Midazolam (0.01mg/kg), inj. glycopyrolate (0.005mg/kg) and inj. fentanyl (3mcg/kg).

In Group A Inj. Esmolol 0.5mg/kg in 30 ml isotonic saline was given IV over 5 min as loading dose 20 min before induction followed by continuous infusion 0.05mg/kg/min until the completion of the surgery.

In Group B 30 ml isotonic saline was given over 5 min as loading dose 20 min before induction followed by continuous infusion of normal saline at same dose and rate as in group A until the completion of the surgery.

Baseline haemodynamic parameters (SBP, DBP, HR, MAP, SpO₂) were noted before induction. Induction was done by inj. Propofol 2mg/kg. Hemodynamic parameters were recorded immediately after induction. Inj. Rocuronium 0.6mg/kg I.V. was given to facilitate tracheal intubation. Intubation was done when complete muscle relaxation achieved. Bilateral air entry checked, position of ET tube confirmed, cuff inflated and tube fixed. Intra operative anaesthesia was maintained with 60% N₂O + 40% O₂ at flow rate of 1lit/min inj. Atracurium 0.1mg/kg I.V. and Desflurane Dial setting (%) was adjusted to maintain BIS between 40 to 60.

We recorded hemodynamic parameters (SBP, DBP, MAP, HR, SPO₂) after intubation at 1 min interval till 5 min then every 5 min interval until the completion of surgery.

Desflurane was discontinued immediately after the last skin stitch. The absolute value of Desflurane MAC delivered to each patient was noted every 5 min. Consumption of desflurane was calculated at the end of surgery by the formula-

Consumption=CFTM/d 2412

Where C=agent dial setting (%)

F=fresh gas flow (liters/min)

T=time (min)

M=molecular weight

d=density of liquid agent (g/ml)

At the end of surgery the fresh gas inflow rate was changed to 1.5 liters /min of oxygen. Inj. neostigmine (0.05mg/kg i.v.) and inj.glycopyrrolate (0.008mg/kg i.v.) were administered to antagonize residual neuromuscular blockade.

We recorded the hemodynamic parameters for 24 hours at 5 min interval for first half hour , 30 min interval for next 4 hours followed by 4 hours interval till 24 hours Post operative pain was measured by VAS score. VAS score recorded every 1 hour till 4 hours and then 4 hourly till 24 hours and time of 1st rescue analgesic (VAS is 3 or more than 3) and total rescue analgesic given in 24 hours was noted. Rescue analgesic used was inj.Tramadol (1mg/kg) IV.

3. Statistics

Statistical analysis was performed with the SPSS, version 21 for windows statistical software package (SPSS inc., Chicago, IL, USA). The categorical data was presented as numbers (percent) and were compared among groups using Chi square test and Anova test. The quantitative data was presented as mean and standard deviation and were compared by student t-test. Probability was considered to be significant if less than 0.05 and highly significant if less than 0.01.

4. Results

Group A (Esmolol) and group B (Saline) were comparable in terms of demographic variables age, sex, weight and duration of surgery (Table 1).

The mean values of Desflurane Dial setting in volume percent to keep BIS between 40 to 60 and Desflurane MAC (Figure 2) were statistically significantly less in group A during intraoperative period .Thus the total consumption of Desflurane concentration required to keep BIS between40 to 60 (Figure 3) was also statistically significantly less in group A (20.4 ml) in comparison to group B (23.6 ml). BIS kept between 40- 60.

The mean values of VAS score (Figure 4) at 0, 1, 2, 3, 4 and 12 postoperative hours were significantly less in group A as compared to group B. Although the mean VAS value at 8 and 24 hours was statistically significantly higher in group A. The first rescue analgesia required (Figure 5) in group A was at 3rd postoperative hour in 17% patients where as in group B 43 (48.9%) patients required analgesia at 2nd postoperative hour. In group A 41(46.6%) patients required analgesic at 4th postoperative hours and 32(36.4%) at 8th postoperative hour. In group B 31(35.2%) patients needed analgesia at 3rd and 14(15.9%) patients demanded it in 4th postoperative hour. The mean total analgesic required in group A was (181.8 mg) which was significantly less than group B (224.4 mg).

The mean values of heart rate (Figure 6) were comparable in both the groups following induction although it remained more settled in group A throughout the intraoperative period and in early postoperative period up to 90 minutes as compared to group B.

The systolic, diastolic as well as mean arterial blood pressure recorded at baseline, following induction, 5 minutes interval during intraoperative period and till 90 minutes in postoperative period was significantly less in group A as compared to group B.

Table 1: Demographic Variables

	Group A (Esmolol)		Group B (Saline)		P value
	Mean	SD	Mean	SD	
Age (yrs)	43.7	8.48	43.4	7.8	0.831 (NS)
Weight (Kg)	55.3	9.4	55.4	8.6	0.164 (NS)
Duration of surgery(min)	28.9	2.5	29.1	2.4	0.781 (NS)

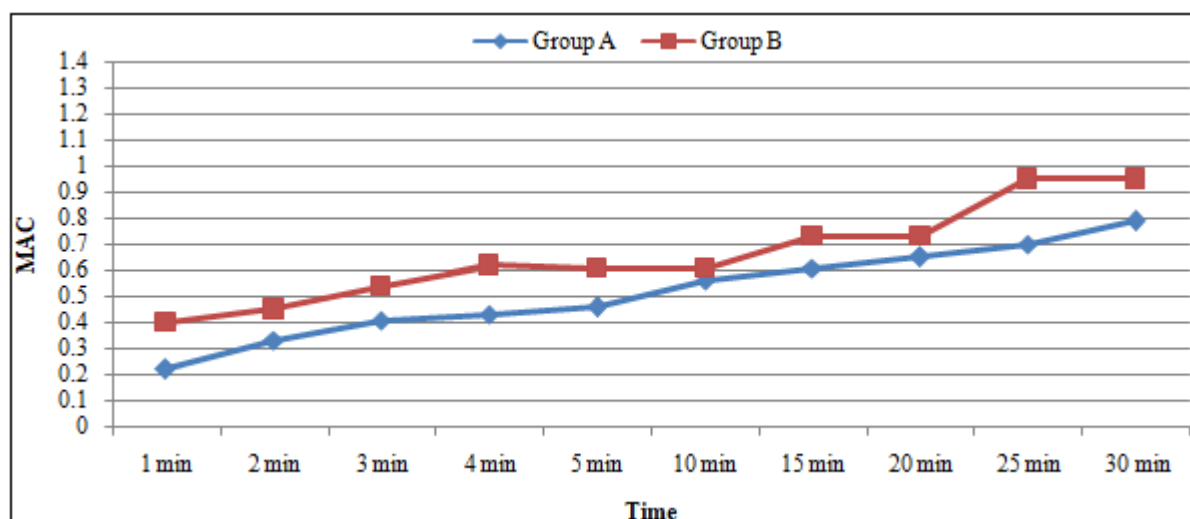


Figure 2: Comparison of Desflurane MAC between the study groups

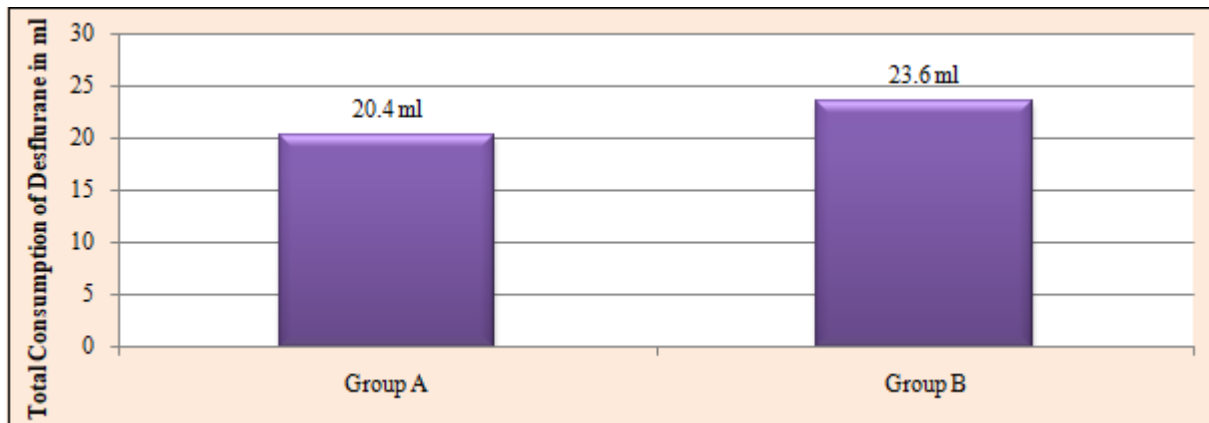


Figure 3: Comparison of total consumption of desflurane (ml)

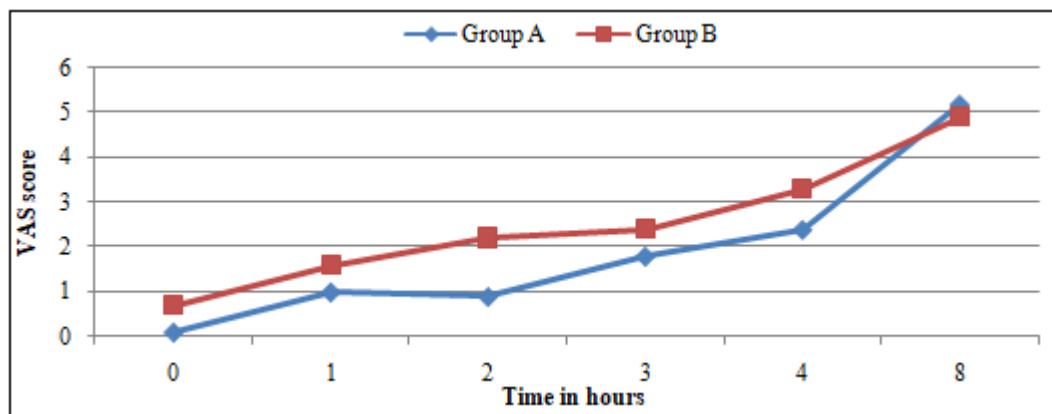


Figure 4: Comparison of VAS score between the study groups

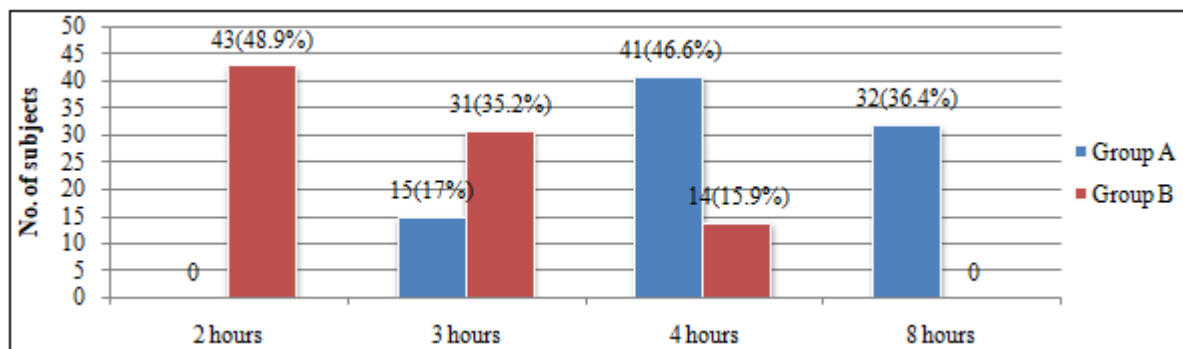


Figure 5: Comparison of time of first rescue analgesic between the study groups

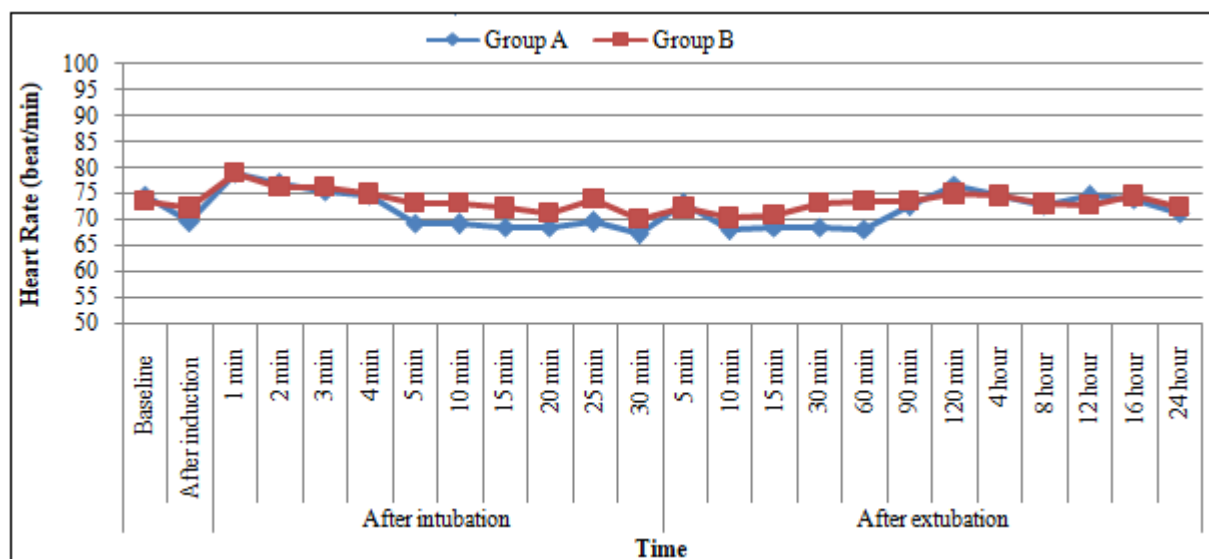


Figure 6: Comparison of Heart Rate between the study groups

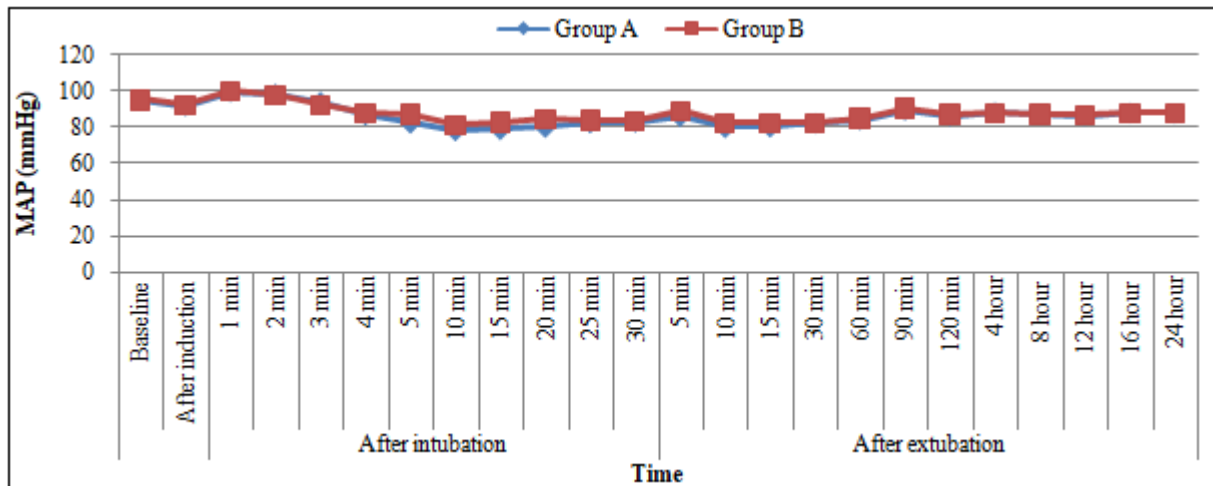


Figure 7: Comparison of MAP between the study groups

5. Discussion

The primary objective of our study was to study effect of beta blocker Esmolol on requirement of inhalation anaesthetics. The underused opioid sparing effect of esmolol in anaesthetic practice and hemodynamic stability were the secondary parameters studied.

The demographic data were comparable in terms of age, sex, weight and duration of surgery so as to ensure that there was no confounding bias.

The mean value of Desflurane delivered in volume percent was aimed to keep BIS between 40 to 60. In our study, the requirement of Desflurane in Esmolol group (group A) was significantly less as compared to saline group (group B). Our results are similar to the study of Chia Y Y et al⁵ who suggested that perioperative esmolol administration during anaesthesia reduces the amount of inhalation anaesthetic used in intraoperative period.

Thus the total consumption of Desflurane (Figure 3) for keeping the BIS between 40-60 was 20.4 ml in group A and 23.6 ml in group B. This showed that Esmolol has anaesthetic sparing effect. The results of our study are well supported by Dereli N et al⁶ who suggested that use of intravenous Esmolol significantly decreases requirement of Desflurane and Propofol. The results of present study are also comparable with Ritima Dhir et al⁷ who concluded that use of Esmolol decreases anaesthetic requirement by modulation of sympathetic component of pain. Our results are not comparable with Bhavna et al⁸ who used entropy instead of bispectral index and concluded that use of Esmolol had no effect on requirement of Desflurane. Johansen JW et al⁹ showed that administration of esmolol with alfentanil decreases minimum alveolar concentration (MAC) of Isoflurane. Our study showed similar results as the total consumption of Desflurane was less in Esmolol group indicating Esmolol decreases MAC of Desflurane.

The explanation of the anaesthetic-sparing effects of Esmolol remains elusive but as an adjunct, it does have an anaesthetic-sparing effect^{6,7}. It has been acknowledged that the blockade of the stress response to noxious stimuli increases the antinociceptive component of anaesthesia. Beta

antagonist act on central nervous system and decrease melatonin secretion, impair memory and vigilance, have anticonvulsant and antinociceptive effect. These actions are probably mediated through attenuation of excitatory neuronal responses in the cingulate gyrus or epileptiform responses in the limbic system¹⁰⁻¹².

The secondary objective studied was opioid sparing effect of Esmolol. Pain was assessed in all the patients as they reached the postoperative room after extubation. The visual analogue scale was used for assessment of pain at 0, 1, 2, 3, 4, 8 and upto 24 hours following extubation in post operative period. The total dose consumption of analgesic for relief of postoperative pain was significantly less in group A (181.8 mg) as compared to group B (224.4 mg). The first rescue analgesic requirement (Figure 5) in group A was 3 hours as compared to group B at 2 hours. None of the patients in group A received rescue analgesia till 2nd postoperative hours, 17% at 3rd hours, 46.6% at 4th hours and 36.4% patients received analgesic at 8th hours. In group B 43% of patients received rescue analgesic as early as 2nd postoperative hours. We observed that mean time of first rescue analgesic requirement was significantly more in group A (5.3 hours) compared to group B (2.7 hours). Similar trends in VAS score were seen in the study by Ritima Dhir et al⁷.

This result of our study is well supported by Dereli N et al⁶ which suggest that use of intravenous Esmolol decreases the post operative pain and analgesic requirement. The results of our study were similar to Chia Y Y et al⁵ in which use of perioperative Esmolol showed significant reduction in total morphine consumption up to 3 post operative days. Bhavna et al⁸ showed significantly less requirement of post operative analgesic morphine in Esmolol group. Systematic review and meta-analysis done by Watts R et al¹³ also shows that Esmolol decreases early postoperative pain intensity, opioids requirement, the requirement of rescue analgesics, and PONV.

The reasons for the opioids sparing properties of Esmolol are unclear. Pain pathways are complex, and it is not clearly understood if the exact mechanism of action for the anaesthetic-sparing effects of esmolol is peripheral or central. Lee SJ et al¹⁴ thought that the decreases in opioids

consumption was related to the decreases in hepatic metabolism of opioids by β -blockers, which prolong the action of the opioids and thereby reduce opioids requirements. Esmolol does slow heart rate; thereby it decreases cardiac output, which decreases hepatic blood flow, so this may slow metabolism of other drugs that are hepatically metabolized, such as fentanyl. **Shukla et al¹⁵** theorized that G proteins, which are involved in nociception, are activated through β -antagonism, which resembles the mechanism of central analgesia.

The mean baseline heart rate was 81.1 ± 4.7 beats/min in group A and 84.2 ± 4.2 beats/min in group B. Although mean values of heart rate increased in both groups following tracheal intubation and then gradually settled down and remained more stable in Esmolol group throughout intraoperative period due to Esmolol infusion (**Figure 6**). Mean values of SBP, DBP and MAP also increased in both groups following tracheal intubation and then gradually settled down and remained more stable in Esmolol group throughout intraoperative period.

In clinical study by **Ritima Dhir et al⁷**, Hemodynamic parameters (HR, SBP, DBP and MAP) increased in response to tracheal intubation and gradually settled after few minutes and remained stable in intraoperative period. Their result was similar to our study. **Bhavna et al⁸** also found similar effect of I.V. esmolol in intraoperative period. In the study by **Dereli N et al⁶**, mean values of heart rate were significantly less in intraoperative period in patients who received Esmolol, however there was no significant difference in intraoperative blood pressure in his study.

After extubation all parameters (HR, MAP, SBP and DBP) increased in response to extubation but were statistically significantly less in Esmolol group. These findings show that Esmolol blunts haemodynamic response of extubation. In the study by **Fuhrman TM et al²**, Esmolol significantly blunted hemodynamic responses of extubation similar to our study.

There was no effect of Esmolol in our study on hemodynamic parameters in late post operative period. This could be explained as we discontinued Esmolol infusion at the completion of surgery and the effect of Esmolol on hemodynamic parameter was weaned off at 2-3 hours of postoperative period. This result of our study was different from study by **Ritima Dhir et al⁷** in which all hemodynamic parameters (HR, SBP, DBP and MAP) remained statistically significantly less in Esmolol group up to 24 hours in post operative period.

In the study by **Dereli N et al⁶**, mean values of heart rate were significantly less in intraoperative periods in patients who received Esmolol and there was no significant difference in post operative recovery periods among all groups.

Depending on these findings we concluded that cardio selectivity and effect on hemodynamic responses of Esmolol is by blocking beta adrenergic responses¹, However effect of Esmolol on hemodynamic parameters was dose dependent and by close hemodynamic follow-up and titrating Esmolol

doses, anaesthesiologists could avoid unwanted side effects of Esmolol like hypotension and also could use this dose titration advantage to decrease intraoperative heart rates, thus decrease myocardial O₂ requirement. No patient in our study showed hypotension and bradycardia.

6. Conclusion

In our study we concluded that IV use of Esmolol reduced the intraoperative use of Desflurane for keeping BIS between 40-60.

Esmolol decreases postoperative pain and delays the rescue analgesic requirement. The total amount of analgesic requirement decreases in postoperative period with intraoperative use of Esmolol. Esmolol also stabilizes intraoperative and early postoperative hemodynamic parameters.

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