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Original Research Article

Comparison of Two Doses of Intravenous Esmolol in Attenuation of Hemodynamic Response to Extubation in Laparoscopic Surgeries

Midur Kumar Sharma[1], Archana Rani[2], Saroz Ahamad[3]

[1]Assistant Professor, Department of General Surgery, Al Fatah School of Medical Sciences and Research, Dhauj, Faridabad, Haryana, India.
[2]Associate Professor, Department of Anaesthesiology and Critical care, Al Fatah School of Medical Sciences and Research, Dhauj, Faridabad, Haryana, India.
[3]Assistant Professor, Department of Anaesthesiology, Rajshree Medical College, Bareilly, UP, India

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Corresponding Author: Dr. Saroz Ahamad
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Abstract:

Background and Objectives: The aim of this study was to compare hemodynamic parameters, including heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure, throughout the extubation time period after the administration of two different doses of intravenous (IV) esmolol.

Material and Methods: This study was a prospective double-blind randomized controlled trial with patients classified as ASA grade I and II, aged between 18 and 65 years, who were scheduled to have an elective laparoscopic surgery under general anaesthesia with endotracheal intubation. A total of sixty participants were randomly assigned to three groups, with each group consisting of twenty individuals. The first two groups were administered intravenous esmolol injections at dosages of 0.5 mg/kg and 1 mg/kg, respectively. The third group got a placebo injection of 10 ml normal saline intravenously when the surgery was completed, prior to extubation.

Results: The demographic data exhibited statistical similarity between the groups. Administering esmolol intravenously at both 0.5 mg/kg and 1 mg/kg effectively reduces the heart rate response. However, a bolus of 1 mg/kg is more efficient than a bolus of 0.5 mg/kg in reducing the blood pressure response during extubation. This higher dose provides more consistent control of hemodynamics both during and after extubation.

Conclusion: Extubation and emergence from general anaesthesia result in substantial elevations in heart rate and blood pressure. It is crucial to focus on reducing this sympathetic response, particularly in patients who are more susceptible to its effects. Administering esmolol intravenously is a successful method for attenuating the heart rate and blood pressure responses during extubation after surgery, while maintaining stable hemodynamics.

Keywords: Attenuation; Esmolol; Extubation; Hemodynamic Response; Stress Response.

Introduction

Hypertension and tachycardia are well-documented events during extubation.[1] These responses could be catastrophic and can lead to complications such as myocardial ischemia, heart failure, cerebrovascular hemorrhage, and pulmonary edema, more so in patients who are hypertensive. Hence, it is of paramount importance to attenuate these hemodynamic responses during extubation.

These hemodynamic responses reflect sympathoadrenal reflex stimulation (epipharyngeal and laryngopharyngeal stimulation) with a concomitant increase in plasma level of catecholamine and activation of alpha- and beta-adrenergic receptors.[2] The development of postoperative hypertension warrants immediate assessment and treatment to reduce the risks of myocardial infarction, arrhythmias, congestive heart failure, stroke, bleeding, and other end-organ damage.[3,4] The response may be attenuated by pharmacological interventions including esmolol (0.51 mg/kg intravenous [IV] 2–5 min before extubation), glyceryl trinitrate, magnesium, propofol infusion, remifentanil/alfentanil infusions, IV lidocaine (1.5 mg/kg over 2 min), topical lidocaine 10%, and perioperative oral nimodipine with labetalol.[5,6]

Several studies suggest that beta-blockers reduce perioperative myocardial ischemia and may decrease the risk of perioperative myocardial infarction and cardiovascular death in high-risk patients.[7,8,9,10] Beta blockers are often used drugs to reduce or treat changes in blood flow

during the time before, during, or after a surgical procedure. Esmolol is a β1-selective adrenergic receptor antagonist that acts quickly and has a brief duration of action. Esmolol possesses characteristics that render it a valuable pharmaceutical agent for the prevention and regulation of sympathetic reactions triggered by harmful stimuli, such as tracheal extubation. Esmolol is used to mitigate the hemodynamic response to extubation, and the favorable impact it has on adverse consequences will promote a broader and more frequent utilization of esmolol during extubation. This intervention aims to mitigate unfavorable consequences during the removal of the endotracheal tube and provide a secure recovery from general anaesthesia.

Aim and Objectives:

To compare the hemodynamic effects of IV administered esmolol in two doses 0.5 mg/kg and 1 mg/kg, in attenuating hemodynamic responses to tracheal extubation and emergence from general anesthesia in patients who have undergone laparoscopic surgeries.

Material and Methods:

This prospective, double-blind, randomized controlled trial was conducted at the Department of Anaesthesiology, at a teaching hospital specializing in tertiary care in North India, after approval from Departmental Dissertation and Institutional Ethics Committee. After written and informed consent, 60 American Society of Anesthesiologists Physical Status of either gender, posted for laparoscopic surgery under general anesthesia was enrolled in the study.

Patients not giving consent, suspected allergy to study drugs (esmolol), difficult airway, history of bronchial asthma or cardiovascular diseases, and patients on β-blockers were excluded from the study.

Sample size calculation:

The investigation established a clinically important difference of 5, as well as a standard deviation of 5, based on the pilot study. To account for attrition in each group, a sample size of 15.68 was rounded off to 20. Using a formula that compares means between groups with 80% power and a 95% level of significance, a total sample size of 60 was calculated. The formula for calculating the sample size was determined based on the comparison of the mean between the two groups, using data from a pilot research with 10 patients in each group.

$n = 2([z\alpha] + z\,[1-\beta])^2\,\sigma^2/d^2$

$Z = 1.96$

$\alpha = 0.05$ (i.e. 95% level of significance), $\beta = 0.2$ (i.e. 80% power)

σ = standard deviation, σ^2 = variance

d = clinically important difference set by the investigator, σ and d based on the pilot study is 5

n = number in each group

Now putting the abovementioned values, n = 15.68 accounting for attrition, n = 20 in each group.

The process of randomization was conducted by employing a computer-generated randomization table. Patients, whose identities were concealed, were then assigned to one of the three groups. The randomization process was conducted by an independent anesthesiologist consultant who was not engaged in data collecting. The consultant prepared the medication, either esmolol or saline, in a syringe with varying dosages. The drug was then supplied to the anesthesiologist responsible for the procedure, disguised in an opaque envelope on the exact day of surgery.

In **Group 0.5**, patients were given a dose of esmolol at a concentration of 0.5 mg/kg. The esmolol was diluted with saline to a total volume of 10 ml and administered intravenously after the surgery was completed and the patient's spontaneous breathing had returned. This was done when the minimum alveolar concentration (MAC) value was less than or equal to 0.3 and the train of four count was 3 or higher.

In **Group 1**, patients were given a dose of esmolol at a concentration of 1 mg/kg. The esmolol was diluted with saline to a total volume of 10 ml and injected intravenously using a 10 ml syringe. The administration took place after the conclusion of surgery, once the patients had resumed spontaneous breathing and reached a minimum alveolar concentration (MAC) value of 0.3 or higher. Additionally, the patients needed to have a train of four count of 3 or greater.

In **Group C**, patients in the control group received a 10 ml saline solution through an intravenous route after the operation was completed and spontaneous breathing efforts had resumed. This was done when the minimum alveolar concentration (MAC) value was equal to or more than 0.3, and the train of four counts was 3 or higher.

Each patient got a comprehensive preanesthetic assessment the day before to their surgical procedure. After transferring the patient to the operating room, standard monitors were connected and initial vital signs were documented. Intravenous access was successfully established.

Following a 3-minute preoxygenation period, general anaesthesia was administered according to the institution's procedure, including the use of neuromuscular blocking and endotracheal intubation. After the operation was finished, the use

of inhalational anaesthetics was gradually reduced and stopped. After reaching a minimum alveolar concentration (MAC) of 0.3, the train of four ratio was assessed using a peripheral nerve stimulator. When the train of four ratio was equal to or greater than 3 and spontaneous breathing resumed after the procedure, residual neuromuscular blockade was counteracted by administering intravenous neostigmine at a dosage of 0.05 mg/kg and glycopyrrolate at a dosage of 0.01 mg/kg. The administration of the study medication occurred subsequent to the reversal. The patient underwent extubation once they began to comply with vocal instructions and exhibited tidal volume breaths of at least 6 mL/kg body weight.

Hemodynamic parameters, including heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure, were measured at multiple time points during the study: before administering the drug, immediately after administration, just prior to extubation, every minute for the first 5 minutes after extubation, and finally at 10 minutes post-extubation.

Any adverse outcomes and the corresponding medical interventions were documented. The suggested treatment for bradycardia, which is defined as a heart rate below 50 beats per minute, is intravenous administration of atropine at a dosage of 0.6 mg. The intended treatment for hypotension, defined as a mean arterial pressure (MAP) less than 20% of the baseline or a systolic blood pressure (SBP) less than 90 mmHg, involved either 200 ml of crystalloid boluses or incremental boluses of 3 mg of IV Mephentermine.

Statistical Analysis: The data analysis was conducted utilizing the Statistical Package for the Social Sciences (SPSS 20 software, IBM India Private Limited, Bangalore, India). The data were examined for normalcy using the Shapiro-Wilk test. The demographic data, including age, weight, height, and body mass index, were subjected to analysis of variance (ANOVA) test assuming a normal distribution. Gender, on the other hand, was analyzed using the Kruskal-Wallis test due to its skewed distribution. The examination of trends in the hemodynamic profile within the group (assuming a normal distribution) was conducted using repeated measures ANOVA. To compare the three separate groups with distinct sets of participants and see if any significant differences exist, a one-way ANOVA was employed in the study. After identifying a substantial disparity, a post hoc Tukey's test was employed to determine the specific source of the discrepancy.

Results

The demographic data exhibited comparability among the groupings. [Table 1]

Table 1: Demographic data

Variables	Group C (n=20) (Mean±SD)	Group 0.5 (n=20) (Mean±SD)	Group 1 (n=20) (Mean±SD)	P-value
Age (in years)	38.71 ± 11.91	40.81 ± 8.51	37.81 ± 8.21	0.605 (NS)
Weight (in Kg)	61.31 ± 7.91	64.91 ± 8.51	60.71 ± 9.91	0.271 (NS)
Height (in cm)	157.71 ± 6.61	158.01 ± 6.21	159.11 ± 8.41	0.821 (NS)
BMI (Kg/m^2)	24.61 ± 3.13	26.01 ± 3.51	23.91 ± 2.91	0.124 (NS)
Gender (M:F)	9:11	8:12	8:12	0.936 (NS)

NS- Not Significant ($p>0.05$)

The average HR values at various time periods during the extubation phase for all three groups are compared, together with their respective standard deviations [Table 2].

The initial heart rate (HR) was similar, however, there were statistically significant variations seen from the moment the medicine was administered until 5 minutes following the removal of the breathing tube. An intergroup comparison was conducted among the three groups. It was observed that there was a statistically significant decrease in heart rate (HR) in both the group of patients from immediately after the administration of medication until the 5th minute following extubation, as compared to the control group. No statistically significant distinction was seen between Group 0.5 and Group 1.

Table 2: Comparison of mean value of heart rate (beats/min) between groups

Time	Group C (n=20) (Mean±SD)	Group 0.5 (n=20) (Mean±SD)	Group 1 (n=20) (Mean±SD)	P-value
Baseline	90.46±10.16	94.11±13.59	98.61±14.35	0.142 (NS)
Immediately after drug administration	102.71±10.88	91.26±9.37	93.16±15.27	0.009 **(S)**
Just before extubation	108.66±10.32	93.01±10.83	89.91±14.22	0.001 **(S)**
1 min post-extubation	109.06±10.97	89.86±11.14	85.56±13.68	0.001 **(S)**
2 min post	108.06±10.25	90.16±10.84	87.31±12.88	0.001 **(S)**
3 min post	107.51±10.67	90.31±10.64	89.51±13.32	0.001 **(S)**

4 min post	107.01±11.45	89.86±10.35	89.46±13.94	0.001 **(S)**
5 min post	104.01±10.86	89.16±10.19	89.61±14.01	0.001 **(S)**
10 min post	87.06±8.84	83.46±7.48	82.36±13.66	0.328 (NS)

NS- Not Significant (p>0.05), S- Significant (p<0.05). Significant statistical findings were seen from immediately after the administration of the medicine to the 10th minute after extubation when comparing the average value and standard deviation of systolic blood pressure (SBP) at different time periods throughout the extubation period across all three groups [Table 3]. Intergroup comparisons revealed a statistically significant decrease in systolic blood pressure (SBP) in Group 0.5 compared to Group C immediately following drug administration, as well as at the 2nd, 3rd, 4th, and 5th minute post-extubation. In contrast, Group 1 consistently showed statistically significant results at almost all time points. Statistically significant differences were seen only during the 1st and 2nd minute after extubation, when comparing Group 0.5 and Group 1.

Table 3: Comparison of mean systolic blood pressure (mmHg) between groups

Time	Group C (n=20) (Mean±SD)	Group 0.5 (n=20) (Mean±SD)	Group 1 (n=20) (Mean±SD)	P-value
Baseline	130.01±16.22	137.01±14.78	136.46±14.98	0.282 (NS)
Immediately after drug administration	143.21±19.23	129.86±16.26	131.31±15.88	0.034 **(S)**
Just before extubation	149.12±23.13	136.31±14.68	126.51±17.18	0.001 **(S)**
1 min post-extubation	146.21±23.07	134.41±16.33	119.11±18.56	0.001 **(S)**
2 min post	149.66±23.21	133.51±19.14	117.71±16.68	0.001 **(S)**
3 min post	150.36±26.12	131.31±14.68	120.41±16.55	0.001 **(S)**
4 min post	149.61±24.45	129.66±13.51	117.71±14.62	0.001 **(S)**
5 min post	146.11±23.21	128.31±15.15	119.81±13.98	0.001 **(S)**
10 min post	134.76±14.28	126.76±10.75	123.36±13.07	0.021 **(S)**

NS- Not Significant (p>0.05), S- Significant (p<0.05). The average values of DBP at various time intervals during the extubation phase for all three groups are compared, together with their respective standard deviations [Table 4]. Significant statistical findings were seen from just prior to extubation until the 5th minute after extubation. When comparing different groups, a significant reduction in diastolic blood pressure (DBP) was seen in Group 0.5 compared to Group C during the 3rd and 4th minute after extubation. In contrast, Group 1 consistently showed statistically significant findings at practically all time periods. Statistically significant differences were seen in Group 0.5 and Group 1 just before to extubation and one minute after extubation.

Table 4: Comparison of mean diastolic blood pressure (mmHg) between groups

Time	Group C (n=20) (Mean±SD)	Group 0.5 (n=20) (Mean±SD)	Group 1 (n=20) (Mean±SD)	P-value
Baseline	82.56±12.91	86.16±9.47	85.96±11.06	0.527 (NS)
Immediately after drug administration	92.26±10.81	84.26±11.05	84.66±14.41	0.075 (NS)
Just before extubation	95.91±16.41	88.31±9.11	76.86±12.92	0.001 **(S)**
1 min post-extubation	93.76±17.17	86.66±9.25	76.16±10.54	0.001 **(S)**
2 min post	93.06±16.64	84.31±10.87	75.86±10.84	0.001 **(S)**
3 min post	94.76±18.53	83.51±9.66	75.61±7.53	0.001 **(S)**
4 min post	91.51±15.65	79.46±8.92	74.01±9.21	0.001 **(S)**
5 min post	86.91±13.52	76.91±9.23	74.71±9.19	0.003 **(S)**
10 min post	81.36±11.83	76.71±8.76	76.56±9.72	0.247 (NS)

NS- Not Significant (p>0.05), S- Significant (p<0.05) The average values of mean arterial blood pressure at various time periods during the extubation period for all three groups, along with their respective standard deviations. **[Table 5]** Significant statistical findings were seen from immediately after the extubation to the 5th minute following extubation. Upon doing intergroup comparisons, it was seen that there was an inconsistent but statistically significant fall in mean arterial blood pressure in Group 0.5 compared to Group C. This decrease was observed at many time points, including shortly before extubation, as well as during the 3rd, 4th, and 5th minute post-extubation. Statistically significant reductions in mean arterial pressures were consistently seen at practically all time periods between Group 1 and Group C. A statistically significant difference was seen between Group 0.5 and Group 1 just prior to extubation, as well as at 1 minute and 2 minutes after extubation. No adverse outcomes were observed in any of the research cohorts.

Table 5: Comparison of mean arterial pressure (mmHg) between groups

Time	Group C (n=20) (Mean±SD)	Group 0.5 (n=20) (Mean±SD)	Group 1 (n=20) (Mean±SD)	P-value
Baseline	98.79±13.18	102.23±11.19	105.24±13.32	0.278 (NS)
Immediately after drug administration	109.61±13.12	98.96±12.87	101.31±14.93	0.043 **(S)**
Just before extubation	113.86±17.02	105.06±10.28	94.41±13.53	0.001 **(S)**
1 min post-extubation	111.69±17.94	103.16±11.28	91.36±13.43	0.001 **(S)**
2 min post	112.24±18.34	102.59±13.19	90.86±10.92	0.001 **(S)**
3 min post	113.89±21.22	99.66±11.94	92.44±10.44	0.001 **(S)**
4 min post	110.31±15.83	97.81±11.16	89.21±9.76	0.001 **(S)**
5 min post	105.84±13.87	95.19±10.28	89.96±9.63	0.001 **(S)**
10 min post	97.79±12.66	93.01±7.63	92.03±8.17	0.145 (NS)

NS- Not Significant ($p>0.05$), S- Significant ($p<0.05$). The assessment of extubation quality was conducted using Eshak's four-point scale and analyzed by the Chi-square test. With a p-value of 0.708, it was determined that there was no significant difference between the groups. Therefore, the administration of intravenous esmolol at either of the dosages did not have an impact on the quality of extubation. [Table 6]

Table 6: Quality of extubation in different groups

Eshak's score	Group C, n (%)	Group 0.5, n (%)	Group 1, n (%)	P-value
0	0 (0)	0 (0)	01 (5)	0.708
1	13 (65)	12 (60)	12 (60)	
2	07 (35)	08 (40)	07 (35)	
3	0 (0)	0 (0)	0 (0)	

NS- Not Significant ($p>0.05$)

Discussion

The primary objective of this study was to examine the reaction to endotracheal extubation and explore the potential for pharmaceutical intervention to reduce its impact. The incidence of problems following tracheal extubation is three times higher than the incidence of complications during tracheal intubation and anaesthesia induction. Pharmacological intervention can help reduce the hemodynamic reactions commonly observed after extubation. Our investigation involved the intravenous administration of esmolol at two distinct dosages in order to mitigate the extubation responses. We then compared the effects of these varying doses of esmolol. There is little evidence supporting the effectiveness of intravenous esmolol in reducing hemodynamic responses, which may help reduce negative occurrences during surgery, such as myocardial infarction and strokes, and lead to favorable outcomes.

In 2014, Alkaya et al. [11] conducted a study to assess the impact of intravenous infusion of esmolol in preventing and managing the hemodynamic response after extubation following elective craniotomy. Hemodynamic parameters among individuals who received esmolol were significantly reduced following esmolol infusion, as compared to the control group after extubation. Therefore, it was deduced that administering a dose of 2 mg/kg esmolol prior to to extubation might reduce the occurrence of high blood pressure and rapid heart rate during extubation after an elective craniotomy. For our research, we employed boluses, which proved to be similarly efficient in attenuating the sympathetic response without causing any notable decrease in blood pressure.

In their study, Nagrale et al [12] examined the hemodynamic impacts of intravenous administration of propofol, lignocaine, and esmolol, administered 2 minutes prior to extubation, in a group of 90 patients. The study determined that intravenous (IV) esmolol is the preferable choice for reducing hemodynamic responses, as opposed to IV propofol and IV lignocaine.

In 2017, Tendulkar and Ninave [13] conducted a randomized control trial (RCT) to examine the impact of intravenous dexmedetomidine with esmolol in minimizing the hemodynamic response during the emergence as well as tracheal extubation. Participants in the esmolol group received an intravenous esmolol bolus of 1.5 mg/kg two minutes before to extubation. In a similar manner, participants in the second group were administered an intravenous bolus of dexmedetomidine at a dose of 0.5 mcg/kg over a period of 10 minutes before to extubation. Therefore, it was shown that both intravenous (IV) esmolol and dexmedetomidine successfully reduce the hemodynamic response. However, IV dexmedetomidine was found to be correlated with greater sedation scores.

In 2019, Ollila et al [14] did a review on the use of intravenous esmolol for cardiac protection during the perioperative phase. Based on three randomized control studies including 196 adult patients, the study indicated that administering intravenous esmolol is a favorable option for preventing

myocardial ischemic variations during the perioperative phase.

In a research done by Prajwal Patel et al [15], a total of 60 patients who were scheduled for elective surgeries were assigned at random into two groups, with 30 patients in each group. Group I received a dose of esmolol at a rate of 1.5 mg/kg, whereas Group II received a dose of labetalol at a rate of 0.25 mg/kg. These doses were given 2 minutes before to extubation, after a usual perioperative anaesthetic treatment. Hemodynamic data obtained include HR, SBP, DBP, and MAP at baseline, reversal, just after administration of research drug, 1 min following research drug, extubation, and at 1, 2, 3, 4, 5, and 15 minutes after extubation. Esmolol demonstrated superior efficacy compared to labetalol for the attenuation of the hemodynamic response at extubation immediately afterwards.

For present study, we administered esmolol intravenously at two different doses: 0.5 and 1 mg/kg. We discovered that while both dosages reduce the degree of tachycardia, administering esmolol at a dosage of 1 mg/kg is more efficient in reducing the blood pressure response during the process of extubation. We observed an increase in systolic blood pressure (SBP) in the control group following extubation, as compared to the first baseline measurement. Patients administered with 0.5 mg/kg of intravenous esmolol observed a reduction in systolic blood pressure (SBP). However, during crucial time moments such as just before extubation and 1 minute after extubation, SBP remained elevated. Patients administered with a dosage of 1 mg/kg of the medication saw a sustained reduction in systolic blood pressure (SBP) at all measured time intervals following drug administration. There was no occurrence of excessive hypotension (30%) in any of the groups. Significant tachycardia was observed in the control group compared to the other groups for duration of up to 10 minutes.

Limitations of the study: The study has several limitations:

- Patients with pre-existing hypertension, who might derive advantages from preventing an elevation in blood pressure following extubation, were excluded from the study.
- Exclusively laparoscopic operations were considered
- The experiment was conducted at a single centre, thus the findings may not be representative of the entire community.

Conclusion

The process of extubation and emergence from general anaesthesia leads to a substantial rise in heart rate and blood pressure. It is crucial to focus on reducing these effects, particularly in patients who are more susceptible to them.

Administering esmolol intravenously at both 0.5 mg/kg and 1 mg/kg effectively attenuates the heart rate response. However, a bolus of 1 mg/kg of esmolol is more effective than a bolus of 0.5 mg/kg in attenuation of the blood pressure response during extubation. This higher dose provides more consistent control over the patient's hemodynamics both during and after extubation.

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