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Original Research Article

Intraoperative Hemodynamic Stability with Esmolol versus Clonidine for Laparoscopic Appendicectomy

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Abstract:

Introduction: Pneumoperitoneum, the introduction of gas into the abdominal cavity, causes disturbances in the body's regulatory systems, affecting acid-base balance, cardiovascular and pulmonary functions, and the stress response. It leads to increased mean arterial pressure, decreased cardiac output, and elevated systemic vascular resistance, potentially impairing tissue and organ perfusion.

Aim and Objectives: To compare the effectiveness, analgesia requirement, and adverse effect of Esmolol and clonidine for maintaining hemodynamic stability in laproscopic appendicetomy.

Material and Methods: In the present prospective comparative study, data was gathered from a total of 90 patients falling within ASA (American Society of Anesthesiologists) categories I and II, who were scheduled for laparoscopic appendicectomy and ranged in age from 15 to 50 years. These patients were selected from CRH Hospital in Himmatnagar, Gujarat, and were divided into both study groups and a control group. The study was conducted over the course of one year, spanning from August 2022 to August 2023.

Result: There is significant difference in the percentage decrease of heart rate from base line value in Esmolol group-E and Clonidine group – C as compared to control. Esmolol Group- E has significantly lower systolic blood pressure as compared to Clonidine Gruop-C and Control Group-D throughout the intra operative period.

Keywords: Esmolol, Clonidine, BP, Heart Rate, Pain.

Introduction

Laparoscopic surgeries have brought about a major transformation in the field of surgical procedures and are widely considered the preferred approach for many operations, often being described as a "gentle surgery." Nevertheless, it's crucial to recognize that this method is not devoid of risks. Notably, it can induce significant hemodynamic alterations, particularly in elderly patients and those with compromised cardiovascular health. [1]

The introduction of pneumoperitoneum, which involves filling the abdominal cavity with gas, exerts a range of effects on the body's various regulatory systems, resulting in disruptions in acid-base equilibrium, cardiovascular and pulmonary functions, as well as the body's stress response. The cardiovascular changes associated with pneumoperitoneum include an elevation in mean arterial pressure, a reduction in cardiac output, and an increase in systemic vascular resistance. These changes can ultimately compromise the perfusion of tissues and vital organs. [2] Various pharmacological substances, including alpha-2 adrenergic agonists, magnesium sulfate, beta-blockers, and opioids, are employed to mitigate the circulatory changes resulting from pneumoperitoneum. Clonidine, a specific alpha-2 adrenergic agonist, leads to a decrease in blood pressure and heart rate, accompanied by reduced systemic vascular resistance and cardiac output. Esmolol, an exceptionally short-acting and selective beta-1 receptor blocker, has been demonstrated to dampen the hemodynamic reactions to noxious stimuli encountered during the perioperative period. [3]

The administration of beta-blockers can effectively manage the adverse effects stemming from excessive sympathetic stimulation. Specifically, beta-adrenergic antagonists offer enhanced control over factors such as cardiac rhythm, myocardial oxygen consumption, and blood pressure, thus serving as a preventive measure against cardiovascular events. Previous research has

indicated that esmolol, which is a cardio-selective beta-1 receptor blocker known for its ultra-short duration of action, can help mitigate hemodynamic alterations triggered by tracheal intubation. Nonetheless, there have been limited studies comparing the effectiveness of esmolol to lidocaine in preventing cardiovascular changes in patients undergoing laryngoscopy and tracheal intubation, and a consensus regarding the appropriate dosage is yet to be established. [4] Taking into account these observations, the current study was structured to assess both the nature and degree of hemodynamic alterations linked to laparoscopic surgery. Additionally, it aimed to determine the effectiveness of clonidine and Esmolol in preventing these hemodynamic changes.

Aim and Objectives

To compare the effectiveness, analgesia requirement, and adverse effect of Esmolol and clonidine for maintaining hemodynamic stability in laproscopic appendicetomy.

Material and methods

In the present study, data was gathered from a total of 90 patients falling within ASA (American Society of Anesthesiologists) categories I and II, who were scheduled for laparoscopic appendicectomy and ranged in age from 15 to 50 years. These patients were selected from CRH Hospital in Himmatnagar, Gujarat, and were divided into both study groups and a control group. The study was conducted over the course of one year, spanning from August 2022 to August 2023.

Inclusion Criteria:

1. Patients categorized as ASA 1 or ASA 2.
2. Patients within the age group of 15 to 50.

Exclusion Criteria:

1. Patients currently receiving treatment with a beta-blocker or calcium channel blocker.
2. Patients with allergies to any of the medications used in the study.
3. Patients with a medical history of hypertension, ischemic heart disease, aortic stenosis, left ventricular failure, or atrioventricular conduction block.
4. Patients who were concurrently taking clonidine, methyl dopa, beta-blocking drugs, benzodiazepines, or MAO inhibitors were also excluded from the study.

Methods

The study followed a randomized prospective comparative design, with randomization carried out using sealed envelopes.

Preoperative Assessment: Detailed medical history was obtained. Thorough clinical examination was conducted. Relevant medical tests, including hemoglobin levels and urine analysis, were performed. Informed consent was obtained from all patients.

Preanesthetic medication included oral ranitidine 150 mg and diazepam 10 mg the night before the surgery. Additionally, intramuscular midazolam 0.03 mg/kg and intramuscular glycopyrrolate 0.2 mg were administered 45 minutes before the surgery. Patients were monitored for oxygen saturation (SpO2), non-invasive blood pressure (NIBP), and ECG on the operation table, with baseline values recorded. Intravenous access was established, and patients were randomly divided into three groups as follows:

Group E: Received Esmolol (0.5 mg/kg as a bolus 5 minutes before anesthesia induction, followed by a continuous infusion of 100 µg/kg/minute throughout the surgical procedure).

Group C: Received Clonidine (3 µg/kg in 100 ml saline as an infusion 15 minutes before anesthesia induction).

Group D: Received a placebo (100 ml of normal saline).

The drug administration was carried out by an anesthesiologist who was not involved in the study to maintain double-blinding. Anesthesia induction involved intravenous administration of Propofol (2 mg/kg), Fentanyl (2 mcg/kg), and succinylcholine chloride (2 mg/kg) for muscle relaxation. A suitably sized cuffed oral endotracheal tube was inserted. Anesthesia was maintained using a mixture of Nitrous Oxide (67%) and Oxygen (33%) with intermittent doses of atracurium and fentanyl. Mechanical ventilation was used, adjusting it to maintain end-tidal carbon dioxide (ETCO2) levels between 30 and 35 mm Hg. The intra-abdominal CO2 pressure was maintained between 13-16 mm Hg. A nasogastric tube was inserted, and gastric suction was applied to empty the stomach after intubation and before extubation.

Hemodynamic instability was defined as a heart rate below 60 beats per minute or a mean arterial blood pressure (MABP) below 75 mm Hg, and any such instability was promptly addressed. Monitoring included the continuous recording of systemic arterial pressure parameters, including systolic, diastolic, and mean arterial pressure, as well as heart rate and oxygen saturation (SpO2) at specific intervals. These intervals were as follows:

- Before anesthesia induction
- Three minutes after endotracheal intubation
- Prior to establishing pneumoperitoneum
- Fifteen minutes after pneumoperitoneum initiation
- Thirty minutes after pneumoperitoneum commencement

- Ten minutes following the release of CO_2.
- Ten minutes after extubation

To reverse muscle relaxation, intramuscular glycopyrrolate at a dosage of 0.01 mg/kg of body weight and intramuscular neostigmine at a dosage of 0.05 mg/kg were administered, and the patient was subsequently extubated. Postoperative pain management included intramuscular tramadol 50 mg on an as-needed basis. The total number of analgesic doses required over a 12-hour period was monitored. Postoperatively, any instances of postoperative nausea and vomiting (PONV) experienced by the patients within the initial 24 hours after anesthesia were documented through direct patient inquiries. These occurrences were assessed using a scale that measured the severity of nausea and vomiting. If a patient exhibited nausea or vomiting, a rescue antiemetic in the form of Metoclopramide (10mg) was administered, and the quantity of doses required was recorded. The postoperative sedation level of the patients was monitored for a 12-hour period using the Ramsay Sedation Score.

Nausea and Vomiting Score:

- No nausea - 0
- No vomiting - 0
- Mild nausea - 1
- Mild vomiting - 1
- Moderate nausea - 2
- Moderate vomiting - 2
- Severe nausea - 3
- Severe vomiting - 3

Ramsay Sedation Score:

- Levels 1-3: Patient awake.
- Level 1: Anxious and agitated or restless, or both.
- Level 2: Cooperative and oriented.
- Level 3: Responds to commands only.
- Levels 4-6: Patient asleep, responds to light. glabellar tap or loud auditory stimulus.
- Level 4: Brisk response.
- Level 5: Sluggish response.
- Level 6: No response.

Statistical Analysis: All data collected from the selected cases were recorded in a comprehensive chart. Computer-assisted data analysis was conducted using the Epidemiological Information Package (EPI 2008) software. This software enabled the calculation of various statistical parameters, including ranges, frequencies, percentages, means, standard deviations, chi-square tests, and 'p' values.

The Kruskal-Wallis chi-square test was employed to assess the significance of differences between quantitative variables, with a 'p' value of less than 0.05 indicating a significant relationship.

Result

The three groups were comparable in patient characteristics like age, sex and duration of surgery.

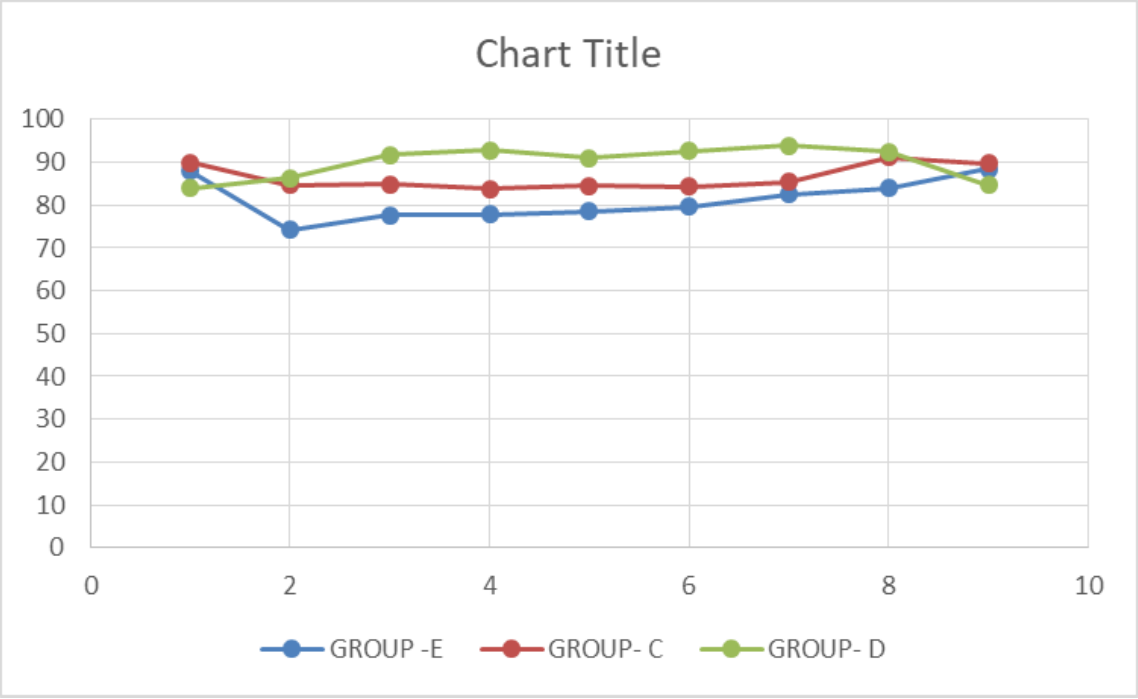

Figure 1: Heart Rate at Different Time Intervals

Fig -1 shows a significant difference in the heart rate between the esmolol and clonidine group as compared with the control group at 1min , 5 min, 15 min ,30 min 45 min and 60 min after intubation. The (Esmolol) Group –E has a lower heart rate as compared to the (clonidine) Group- C and the Control Group – D

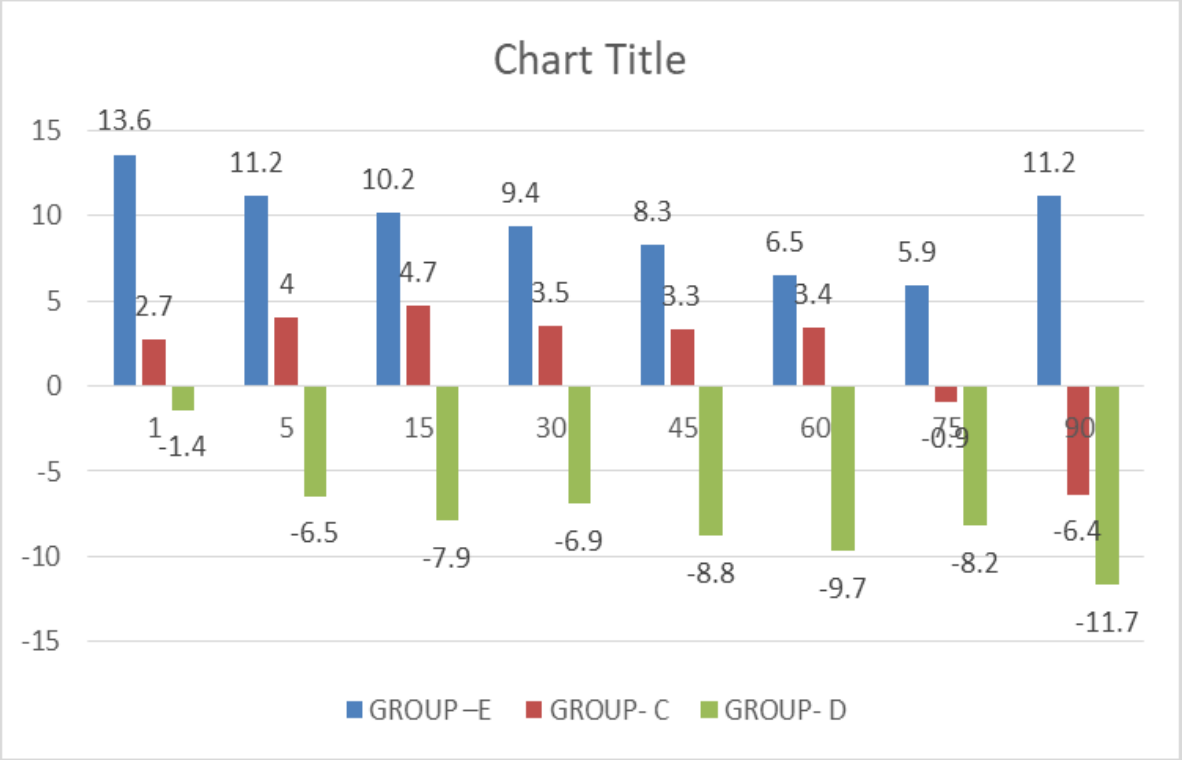

Figure 2: Percentage Change in Heart Rate from Base Line (PI) at Different Time Interval

Fig 2- shows a significant difference in the percentage decrease of heart rate from base line value in Esmolol group-E and Clonidine group – C as compared to control.

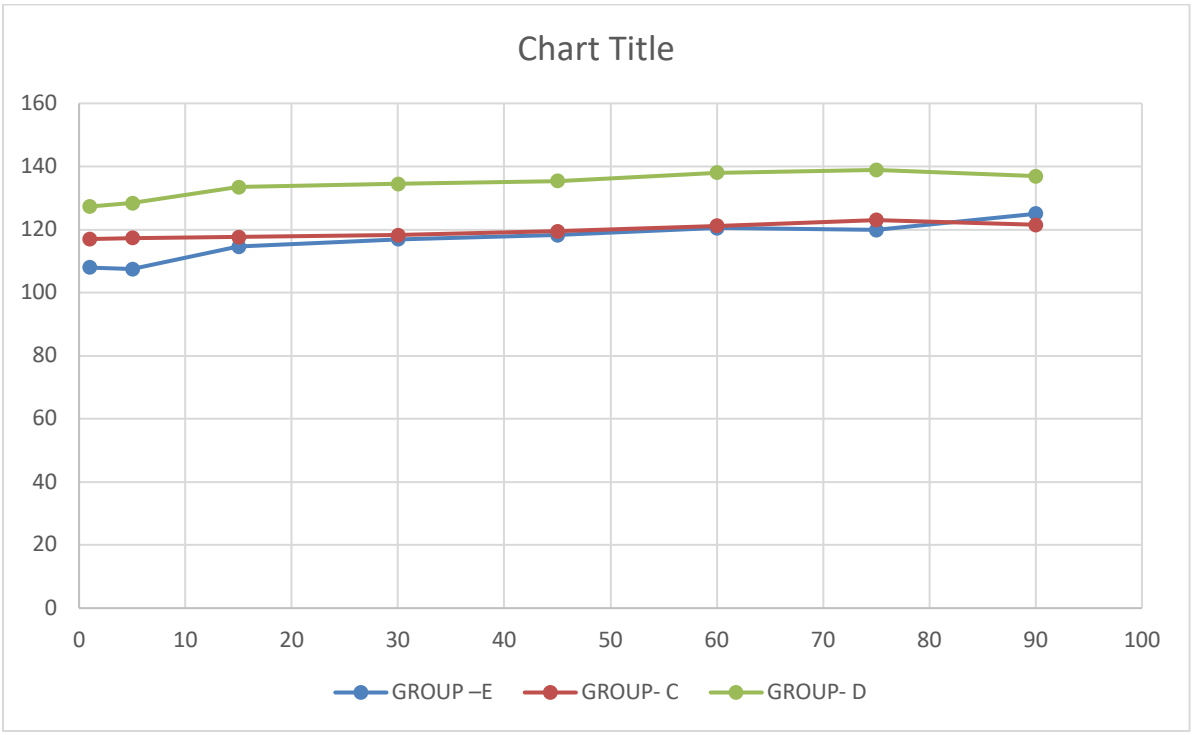

Figure 3: Systolic Blood Pressure at Various Time Interval

Figure 3 - shows that there is a significant difference in the systolic blood pressure between the study groups and the control groups throughout the intra operative period. Esmolol Group- E has significantly lower systolic blood pressure as compared to Clonidine Gruop-C and Control Group-D throughout the intra operative period.

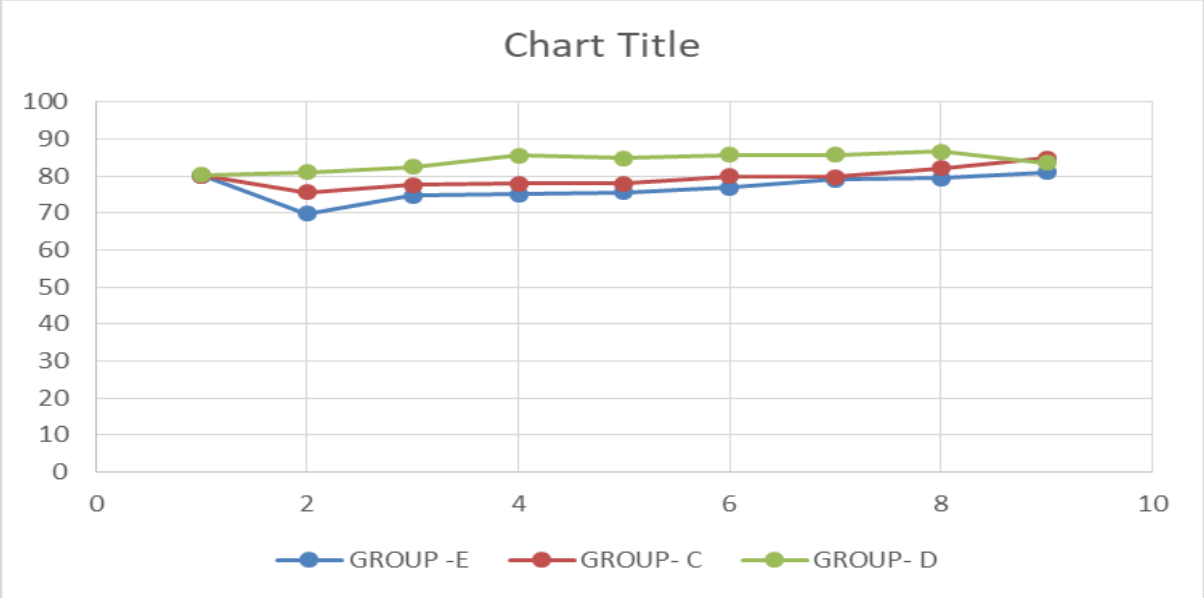

Figure 4: Diastolic Blood Pressure at Various Time Intervals

Figure 4 - shows that there is a significant difference in the diastolic blood pressure between the study groups and the control groups throughout the intra operative period. Esmolol Group- E has lower systolic blood pressure as compared to Clonidine Gruop-C and Control Group-D throughout the intra operative period.

Table 1: post-operative requirement of various drugs

	Group – E	Group - C	Group – D	P value
Fentanyl requirement	109.7±18.8	110.3±16.7	116.7±14.7	0.14
Anti-emetic doses	0.77±0.68	0.97±0.41	1.07±0.37	0.047
Scoring Of Nausea And Vomiting	1.83±0.71	1.97±0.41	2.07±0.37	0.18
Analgesic Requirement	1.9±0.55	1.57±0.63	2.4±0.5	0.001

The table compares post-operative drug requirements among three groups: Group E, Group C, and Group D. Fentanyl requirement shows minimal variation between the groups, with no statistically significant difference ($p = 0.14$). However, anti-emetic doses exhibit a significant difference ($p = 0.047$), with Group D requiring the highest doses. Scoring of nausea and vomiting shows slight differences among the groups but no statistically significant variance ($p = 0.18$). Interestingly, analgesic requirement significantly differs among the groups ($p = 0.001$), with Group D requiring the highest amount compared to Groups E and C.

Table 2: Sedation score at different time interval

Sedation Score at	Group E	Group C	Group - D	P value
1	2.47±0.68	3.07±0.78	2.47±0.82	0.003 significant
4	2.27±0.58	2.53±0.63	2.07±0.27	0.0016 significant
6	2.1±0.4	2.1±0.4	2.03±0.18	0.7998 not significant

Table 2 presents sedation scores at different time intervals for three groups: Group E, Group C, and Group D. At 1 and 4 hours post-operation, there are significant differences in sedation scores among the groups ($p = 0.003$ and $p = 0.0016$, respectively).

Specifically, Group C shows higher sedation scores compared to the other groups at these time points. However, by the 6-hour mark, there is no significant difference in sedation scores among the groups ($p = 0.7998$), indicating convergence in sedation levels over time.

Discussion

Pneumoperitoneum during laparoscopy produces significant haemodynamic changes, which can be detrimental especially in elderly and hemodynamically compromised patients.

Various techniques and pharmacological agents have been used to counteract these detrimental effects of pneumoperitoneum.

This double blind prospective study was carried out in 90 adult patients, to evaluate the effect of

Esmolol and clonidine in attenuating haemodynamic stress response associated with pneumoperitoneum. Esmolol is the first intravenous, short-acting, titratable β-blocker available for use in critical care and surgical settings. Esmolol is thought to be a “jack

Clonidine is often referred to as the "jack of all trades" among anesthesia drugs because of its capability to both prevent and manage cardiovascular responses triggered by perioperative stimuli. Various studies utilizing intravenous clonidine have demonstrated its effectiveness in averting hemodynamic disturbances resulting from events such as intubation and laparoscopic cholecystectomy.

Nonetheless, it's important to note that administering higher doses of clonidine has been associated with the occurrence of pronounced bradycardia and hypotension. For instance, Malek et al. [5] used 150 micrograms of clonidine as an intravenous infusion, while Sung et al. [6] and Yu et al. [7] employed 150 micrograms of oral clonidine as premedication to maintain hemodynamic stability during pneumoperitoneum. In fact, Yu et al. [7] even recommended the routine use of clonidine as premedication in laparoscopic surgeries. Another study conducted by Das et al. [8] involved the use of 150 micrograms of oral clonidine administered 90 minutes before surgery to prevent hemodynamic responses to pneumoperitoneum in laparoscopic cholecystectomy. Additionally, Kalra et al.[9] administered clonidine intravenously at a rate of 1 microgram per kilogram over a 15-minute period before pneumoperitoneum, with the clonidine group displaying significantly superior control over hemodynamics compared to the control group

Various researchers have explored the use of beta-adrenergic receptor antagonists in surgical procedures to mitigate the stress response associated with intubation and minimize undesirable hemodynamic changes during surgery. Esmolol, a selective beta-adrenergic receptor blocker known for its rapid action, was employed in this study. A bolus dose of 0.5 mg/kg of Esmolol was administered 5 minutes prior to anesthesia induction, followed by a continuous infusion of 100 µg/kg/minute throughout the surgical procedure. The results revealed a significant and consistent decrease in heart rate throughout the procedure, with a mean value of 78.5 ± 10.9. The heart rate ranged from 75.1 ± 10.4 to 88.5 ± 13.0, and the percentage reduction from the baseline value (pre-induction) varied from a mean value of 13.6 ± 7.2 to 6.5 ± 10.5. Among the 30 cases studied, 3 patients experienced bradycardia with a heart rate below 60, necessitating a reduction in the Esmolol infusion dose.

Furthermore, there was a significant difference in systolic blood pressure between the Esmolol group and the control group throughout the procedure. The mean systolic blood pressure was 116.9 ± 12.5, with a range of 108 ± 13.2 to 125 ± 4.2. The observed percentage reduction in mean systolic blood pressure was 5.4 ± 9.8, with a maximum reduction of 12.9 ± 6.7.Additionally, there was a notable difference in diastolic blood pressure, with a mean blood pressure of 75.7 ± 7.1, ranging from 69.9 to 81.0

Ozturk et al [10] previously noted an opioid-sparing effect when Esmolol was used intraoperatively. However, in my study, there was no significant reduction in the intraoperative fentanyl requirement.

Studies conducted by Ozturk et al [10], White et al [11], and Lee and Lee [12] demonstrated that intraoperative administration of Esmolol led to a decrease in postoperative analgesic or opioid requirements. In this study we observed a substantial reduction in the postoperative analgesic requirement among patients who received intraoperative Esmolol compared to the control group. The mean requirement was 1.9 ± 0.55 for the Esmolol group and 2.4 ± 0.5 for the control group. The hippocampus, known for its involvement in nociception, plays a role mediated by N-methyl-D-aspartate receptors. It's possible that the activation of hippocampal β-adrenergic receptors may impact nociceptive processes. Blocking these receptors could potentially reduce the contribution of β-adrenergic activation to the perception of pain intensity.

Clonidine, an imidazoline derivative, is a selective α2 adrenergic agonist with potent antihypertensive properties. It induces a decrease in heart rate and blood pressure, accompanied by reduced systemic vascular resistance (SVR) and cardiac output. Clonidine inhibits the release of catecholamines and vasopressin, thus modulating the hemodynamic changes induced by pneumoperitoneum.

Aho et al employed doses of 3 µg/kg and 4.5 µg/kg of clonidine to suppress the hemodynamic response to pneumoperitoneum. Joris et al used a notably high dose of clonidine (8 µg/kg) to lower catecholamine and vasopressin levels following pneumoperitoneum. Malek et al administered 150 µg of clonidine intravenously and intramuscularly, while Sung et al and Yu et al utilized 150 µg of oral clonidine as premedication to maintain hemodynamic stability during pneumoperitoneum.

In the present study an infusion of 3 µg/kg of Clonidine 15 minutes before induction, resulting in a noteworthy decrease in heart rate throughout the intraoperative period, with a mean of 84.6 ± 9.7. The heart rate ranged from 83.6 ± 10.3 to 91.3 ± 10.1. Moreover, there was a significant difference

in the percentage decline from the pre-induction value, with a mean percentage fall of 4.7 ± 12.6.

There is a significant reduction in systolic blood pressure compared to the control group, with a mean systolic blood pressure of 118.2 ± 10.5. The systolic blood pressure ranged from 117 ± 12.8 to 123.4 ± 12.1. There was a significant percentage decrease in systolic blood pressure from the baseline pre-induction value compared to the control group, with a mean percentage decrease of 3.8 ± 8.0, and a maximum reduction of 4.9 ± 8.5.

Additionally, there was a significant reduction in diastolic blood pressure compared to the control group, with a mean of 78.0 ± 8.3, ranging from 75.6 ± 8.3 to 84.9 ± 3.0. Clonidine's interaction with endogenous opioids, particularly beta-endorphins, was observed. Laparoscopy resulted in a significant increase in plasma beta-endorphins. Clonidine's impact on hemodynamics and plasma beta-endorphins may indicate a deeper level of anesthesia in those who received Clonidine. There is reduction in the incidence of postoperative nausea and vomiting (PONV) in patients who received Clonidine, with a mean antiemetic requirement of 0.97 ± 0.41, in contrast to the control group with a mean value of 1.07 ± 0.37. Among the 30 patients who received Clonidine, 10 did not require any antiemetic, and 2 patients needed two doses of antiemetics.

Previous research by Das Marimony et al [8] also observed a decreased incidence of nausea and vomiting in patients receiving Clonidine. Clonidine's ability to reduce sympathetic outflow while enhancing parasympathetic outflow from the central nervous system results in increased gastrointestinal motility. Although the antiemetic properties of Clonidine have been reported by several researchers, further investigation is needed to understand the mechanism by which it functions.

Sung et al [6] and Yu et al [7] demonstrated that preoperative administration of Clonidine reduced postoperative analgesic requirements. Similarly, in my study, patients who received Clonidine displayed a significant reduction in postoperative analgesic requirements. The mean analgesic dose required was 1.57 ± 0.63, compared to the control group, which required 2.4 ± 0.5

Das Marimony et al [8] found a decreased incedence of nausea and vomiting in patients receiving Clonidine. Clonidine increases gastrointestinal motility by decreasing sympathetic outflow and increasing parasympathetic outflow from the central nervous system. Although many workers have reported the antiemetic property of clonidine, the mechanism by which it acts warrants further investigation. Sung et al [6] and Yu et al [7] found that preoperative clonidine admistration reduced the post-operative analgesic requirement. In my study there was a significant reduction in the post-operative analgesic requirement in patients receiving clonidine. The mean analgesic dose requirement was 1.57 ± 0.63 as compared to control group requiring 2.4 ± 0.5. In my study the post-operative sedation score was observed for 6 hrs postoperatively and was found that clonidine group had a significantly high sedation score at 1 hr and 4 hr after the surgery. The mean sedation score at 1 hr was 3.07 ± 0.78 and at 4 hrs 2.53 ± 0.63. When compared with Esmolol and clonidine the intraoperative heart rate, systolic BP, Diastolic BP was better maintained with Esmolol Group Than with the clonidine Group. The mean heart rate maintained in the range of 75.1 ± 10.4 to 88.5 ± 13.0 in the Esmolol group and 83.6 ±10.3 to 91.3 ± 10.1in the clonidine group. The mean systolic BP in Esmolol group was in the range of 108 ±13.2 to 125 ± 4.2 and in clonidine group was in the range of 117 ± 12.8 to 123.4 ± 12.1. It was found to be statistically significant. It was observed that post-operative anti emetic requirement was significantly less in both Esmolol and Clonidine group. The requirement was more reduced in the Clonidine group as compared to Esmolol group, but the difference was not found to be statistically significant.

Post-operative analgesic requirement was also observed to be significantly lower in Esmolol and Clonidine group as compared to the control group. It was found to be more decreased in clonidine group than with Esmolol group, but the comparison found no significant statistical significance. Post-operative sedation was more with clonidine group as compared to Esmolol and Control group. Esmolol group did not have any significant increase in the post-operative sedation as compared to control. No adverse effect was observed with the study group during the intra operative and post-operative period.

Some limitations with the design of the study. First, the anaesthesiologists who administered the anaesthetics might have been biased in the administration of the study drugs. Second, it is argued that the use of a BIS monitor would have ensured that the three groups had similar depth of anaesthesia.

References

1. Alkatout I, Mechler U, Mettler L, Pape J, Maass N, Biebl M, Gitas G, Laganà AS, Frey-tag D. The Development of Laparoscopy-A Historical Overview. Front Surg. 2021 Dec 15; 8:799442.
2. Srivastava A, Niranjan A. Secrets of safe lapa-roscopic surgery: Anaesthetic and surgical considerations. J Minim Access Surg. 2010 Oct; 6(4):91-4.

3. Giovannitti JA Jr, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. Anesth Prog. 2015 Spring; 62(1):31-9.
4. Grandi E, Ripplinger CM. Antiarrhythmic mechanisms of beta blocker therapy. Pharmacol Res. 2019 Aug; 146:104274.
5. J. Malek, J. Knor, A. Kurzova, M. Lopourova Adverse hemodynamic changes during laparoscopic cholecystectomy and their possible suppression with clonidine premedication. Comparison with intravenous and intramuscular premedication, Rozhl Chir, 1999;78: 286-29
6. C.S. Sung, S.H. Lin, K.H. Chan, W.K. Chang, L.H. Chow, T.Y. Lee Effect of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy, Acta Anaesthesiol Sin, 2000; 38: 23-29.
7. H.P. Yu, S.S. Hseu, H.W. Yien, Y.H. Teng, K.H. Chan, Oral clonidine premedication preserves heart rate variability for patients undergoing laparoscopic cholecystectomy, Acta Anaesthesiol Scand, 2003;47: 185-190.
8. Das Mrinmoy, Ray Manjushree, Mukherjee Gauri, Hemodynamic changes during laparoscopic cholecystectomy: effect of oral clonidine premedication, Indian J Anaesth, 2007;51: 205-210.
9. N.K. Kalra, A. Verma, A. Agarwal, H.D. Pandey, Comparative study of intravenously administered clonidine and magnesium sulfate on hemodynamic responses during laparoscopic cholecystectomy, J Anaesthesiol Clin Pharmacol, 2011;27: 344-348.
10. Ozturk T, Kaya H, Aran G, Aksun M, Savaci S. Postoperative ben-eficial effects of esmolol in treated hypertensive patients undergoing laparoscopic cholecystectomy. Br J Anaesth. 2008;100(2):211-214
11. White PF, Wang B, Tang J, Wender RH, Naruse R, Sloninsky A. The effect of intraoperative use of esmolol and nicardipine on recovery after ambulatory surgery. Anesth Analg. 2003;97(6):1633-1638
12. Lee S-J, Lee J-N. The effect of perioperative esmolol infusion on the postoperative nausea, vomiting and pain after laparoscopic appendectomy. Korean J Anesthesiol. 2010; 59(3): 179-184.