A Randomized Controlled Study to Compare Hemodynamic Effects between Clonidine and Pregabalin in Laparoscopic Cholecystectomy

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Abstract

Background: Laparoscopic cholecystectomy (LC) is associated with pneumoperitoneum and hemodynamic disturbances. Pregabalin and Clonidine have been used for anesthetic effects, but a better drug for controlling hemodynamic parameters is being investigated. Aims: The study was done to assess and compare the efficacy of preoperative single oral dose of pregabalin and clonidine in maintaining the hemodynamic parameters in the LC. Settings and Design: The prospective, interventional, randomized, comparative, single-blinded study was conducted in the department of anesthesia and surgery from January 2015 to September 2016 after taking approval from the institutional ethical committee. Materials and Methods: The study included a total of 90 patients, aged between 18 and 56 years of both sexes scheduled for elective LC. Patients were randomized into three groups of 30 each who received oral pregabalin 150 mg, clonidine 200 ug, and placebo. The hemodynamic parameters were recorded at various time intervals along with any adverse events. Statistical Analysis: Quantitative variables were compared using unpaired t-test (when the data sets were not normally distributed) between the two groups. Qualitative variables were compared using Chi-square test/Fisher’s exact test. P < 0.05 was considered statistically significant. Results: There was a significant increase in the heart rate (HR) and systolic, diastolic, and mean blood pressure during laryngoscopy and pneumoperitoneum in the control group as compared to both pregabalin and clonidine. HR was significantly lower in clonidine group after extubation and in postoperative period than both control group and pregabalin group. There was no major difference in the incidence of side effects. Conclusion: Both pregabalin (150 mg) and clonidine (200 ug) were effective in controlling the hemodynamic parameters during LC, with clonidine providing better hemodynamic stability than Pregabalin.

Keywords: Clonidine, hemodynamic parameters, laparoscopic cholecystectomy, laryngoscopy, pneumoperitoneum, pregabalin

INTRODUCTION

Laparoscopic cholecystectomy (LC) has been pursued in comparison to open surgery and has become the gold standard since its first inception in 1987.[1] The advantages offered include small scar, short surgery, and early discharge from the hospital.[2] Though the cost is slightly higher due to the use of specified instruments and the technique, the insurance coverage makes it a relatively affordable surgery. However, pneumoperitoneum is a common side effect of LC, which is required for a proper visualization of the surgical area and certain operative manipulations.

Pneumoperitoneum affects several homeostatic systems leading to alteration in acid-base balance, cardiovascular, pulmonary physiology and stress response such as increase in mean arterial pressure (MAP), decrease in cardiac output, and increase in systemic vascular resistance which causes decreased tissue perfusion.[3,4] The relative chances of such hemodynamic disturbances during LC are much higher as compared to other types of laparoscopic surgeries due to the unique steep head-up position which is required to be maintained during LC. In addition to the creation of the pneumoperitoneum, endotracheal intubation as required for ventilation also increases hemodynamic instability.

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during LC is also an invasive procedure that may cause intense autonomic response. Tachycardia, hypertension, arrhythmias, and myocardial ischemia are induced by intubation.\[5\]

The primary aim of the anesthetic management during such surgeries is to stabilize the hemodynamic parameters including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP along with optimal levels of analgesia.\[5\]

The increasing demand of LC led to surge in the search for pharmacological agents that may help stabilize the HR and BP in response to pneumoperitoneum and intubation. Many drugs including opioids, local anesthetics, adrenergic blocking drugs, and vasodilators have been used to attenuate the response but attained a variable success rate with few disadvantages such as headaches and prolonged anesthesia leading to delayed discharge.\[5,6,7\]

Pregabalin and clonidine are the two drugs which have been studied widely for postoperative analgesia, but there are very few studies that evaluated their use as oral premedication for attenuation of pressor response.\[8-10\]

Clonidine is a selective α2 agonist, which is opioid sparing and decreases HR and blood pressure. It has been used for attenuating vasopressor responses in previous observational studies.\[11-13\] Pregabalin, on the other hand, is a derivative of the neurotransmitter γ-aminobutyric acid (GABA) that possess analgesic, anxiolytic, anticonvulsant, and hemodynamic stabilizing properties.\[14-16\] Both drugs can be given orally and are equally good, but the definitive choice among the two remains a matter of choice by the anesthesiologist rather than on evidence-based results.

The present study was thus conducted to study the efficacy of oral premedication with pregabalin or clonidine on changes in HR and mean arterial blood pressure during laryngoscopy and laparoscopy, along with perioperative hemodynamic stability.

**Materials and Methods**

The prospective, interventional, randomized, comparative, single-blinded study was conducted in the department of anesthesia and surgery from January 2015 to September 2016. Approval was taken from the institutional ethical committee. After taking written informed consent from the patients, a total of 90 American Society of Anaesthesiologists (ASA) Grade I or II normotensive patients aged 18–56 years and scheduled for elective surgery under general anesthesia were recruited for the randomized comparative study.

Block randomization with sealed envelope system was chosen to randomize the study patients. Fifteen randomly generated treatment allocations within sealed opaque envelopes assigning A, B, and C in 5 envelopes each were prepared, where A represented oral pregabalin group, B represented oral clonidine group, and C represented control group. Once a patient gave consent to enter a trial, an envelope was opened, and the patient was offered the allocated group. In this technique, patients were randomized in a series of blocks of fifteen. The patient was not aware as to which treatment he/she is getting, making the study single blinded.

The patients were assigned randomly into either of following groups with each group comprising 30 patients:

- Group A patients received preoperative oral pregabalin 150 mg 1 h before surgery
- Group B patients received preoperative oral clonidine 200 μg 1 h before surgery
- Group C patients did not receive any preoperative drug (control group).

The study of Mrinmoy et al.\[3\] observed that rise in HR, SBP, DBP, and MAP was 81.26 ± 8.40 bpm, 119.6 ± 10.06 mm Hg, 81.26 ± 8.40 mm Hg, and 93.83 ± 8.107 mm Hg, respectively, in the clonidine group. Taking these values as reference and assuming difference of 10% in change in hemodynamic parameters between clonidine and control/pregabalin, the minimum required sample size with 90% power of study and 5% level of significance is 23 patients in each study group. To reduce margin of error, total sample size taken is 90 (30 patients per group).

Formula used is:

For comparing mean of two groups

\[
N \geq \frac{(\text{standard deviation})^2 \times (Z_a + Z_b)^2}{(\text{mean difference})^2}
\]

where \(Z_a\) is value of \(Z\) at two-sided alpha error of 1% and \(Z_b\) is value of \(Z\) at power of 90% and mean difference is difference in mean values of two groups.

The following eligibility criteria were followed:

**Inclusion criteria**

1. Written informed consent by the patient’s relative
2. ASA risk I and II.
3. Patients aged 18–56 years of either sex
4. Patients scheduled for elective surgeries under general anesthesia.

**Exclusion criteria**

1. Patient refusing to give consent
2. Allergy to pregabalin, clonidine
3. Patients with anticipated difficult intubation
4. Patient having a preexisting neurological disease/ seizure disorder or any increased intracranial pressure (hydrocephalus, head injury)
5. Patients under treatment by steroids, nonsteroidal anti-inflammatory drugs or opioids before surgery
6. ASA status III, IV, V
7. Emergency surgeries
8. Patients with history of asthma, hypertension, diabetes, severe coronary artery disease, myocardial infarction, renal disease, coagulopathy, or bleeding disorder.
On the previous day of surgery, detailed history of the patients was taken; physical examination and routine investigations (complete blood count, renal function test, liver function test, serum electrolytes, chest X-ray, electrocardiogram) were performed. Before 1 h of surgery, Group A patients were given tablet pregabalin 150 mg orally and Group B patients were given tablet clonidine 200 ug orally with a sip of water. Group C patients received none of these. In the operating room, routine monitoring was done. The interventional medications were procured by indenting from the hospital pharmacy and thus were identical. A standard uniform protocol for premedication drugs, induction agents, muscle relaxants, and maintenance of anesthesia were administered in all the patients and the groups.

Patients were induced with fentanyl 3 ug.kg$^{-1}$ and propofol 2 mg.kg$^{-1}$; orotracheal intubation was facilitated by vecuronium 0.08 mg.kg$^{-1}$. Anesthesia was maintained with 100–200 mg.kg$^{-1}$.min$^{-1}$ propofol infusion and 66% nitrous oxide in oxygen. At the end of surgery, residual neuromuscular paralysis was antagonized with neostigmine 0.05 mg.kg$^{-1}$ and glycopyrrolate 0.01 mg.kg$^{-1}$. On the recovery of the patients, they were extubated and taken to the postanesthesia care unit (PACU). In the PACU, patients received intravenous fentanyl via patient controlled analgesia with patient activated dose of 20 mg, lockout interval of 5 min, with a maximum allowable fentanyl dose being 2 g.kg$^{-1}$.h$^{-1}$.

Intraoperatively, HR, MAP, SBP, and DBP levels were monitored and recorded before and after induction, immediately after intubation and 1, 5, and 15 min after laryngoscopy and endotracheal intubation, after insufflation and after 5, 15, 30, and 45 min of insufflation, after exsufflation, at extubation and postop 10 min. Patients were observed for complications and treated as required.

All patients were observed for possible complications or side effects for a minimum period of 24 h postoperatively. Sedation was assessed using the Ramsay Sedation Scale after pretreatment with the study drugs in both the groups. Scoring was done just before induction of anesthesia.

**Statistical analysis**

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± standard deviation. Quantitative variables were compared using unpaired t-test (when the data sets were not normally distributed) between the two groups. Qualitative variables were compared using Chi-square test/Fisher’s exact test. $P < 0.05$ was considered statistically significant. The data were entered into Microsoft EXCEL spreadsheet and analysis were done using Statistical Package for the Social Sciences (SPSS) version 21.0 IBM, Chicago (USA).

**Results**

A total of 90 patients were included in the study. Baseline characteristics are given in Table 1. Mean age was $40.8 \pm 11.03$ years in Group A, $38.4 \pm 11.42$ years in Group B, and $39.4 \pm 12.40$ years in Group C. There was no statistically significant difference of age among the 3 groups. Majority of the patients were in ASA Grade 1 in all the groups. The baseline characteristics were comparable among the three groups.

On the Ramsay sedation scale, in Group A, 27 patients scored 2; in Group B, all patients scored 2, and in Group C, all 30 patients scored 1. In our study, all the patients were awake irrespective of the groups when they were brought to the operating room.

The values of HR at preinduction, after giving premedication, and at the time of induction were comparable between three groups with no significant difference. There was statistically significant difference in HR during laryngoscopy and intubation, and up to 5 min after that between Group A and Group B, and Group B and Group C. There was statistically significant difference in HR during insufflation and during intraoperative period between Group A and Group C, Group B and Group C, and Group A and Group B. There was no statistically significant difference in HR at time of exsufflation, extubation and in postoperative period between Group A and Group C whereas HR was significantly lower in Group B when compared with Group C [Table 2].

The values of SBP at preinduction, after giving premedication and at the time of induction were comparable between three groups with no significant difference. There was statistically significant difference in SBP during laryngoscopy and intubation between Group A and Group B and Group C. There was statistically significant difference in SBP during insufflation and during intraoperative period between Group A and Group C, Group B and Group C and Group A and Group B. There was no statistically significant difference in SBP at time of exsufflation, extubation between Group A and Group C whereas SBP was significantly lower in Group B when compared with Group A and Group C at the time of exsufflation [Table 3].

The values of DBP at preinduction, after giving premedication and at the time of induction were comparable between three groups with no significant difference. There was statistically significant difference in DBP during laryngoscopy and intubation between Group A and Group B and Group C. There was statistically significant difference in DBP during insufflation and during intraoperative period between Group A and Group C, Group B and Group C and Group A and Group B. There was no statistically significant difference in DBP at time of exsufflation, extubation between Group A and Group C whereas DBP was significantly lower in Group B when compared with Group A and Group C at the time of extubation [Table 4].

The values of mean blood pressure at preinduction, after giving premedication and at the time of induction were comparable between three groups with no significant difference. There was statistically significant difference in MBP during laryngoscopy and intubation between Group A and Group B and Group B and
In the present study, we found that both pregabalin or clonidine are effective in maintaining the hemodynamic stability during laryngoscopy and LC with minimal side effects, with clonidine providing a better hemodynamic stability than Pregabalin.

All patients selected in the study belonged to the age between 18 and 55 years. The mean age of patients in group A, B, and C were 40.8 years, 38.4 years, and 39.4 years, respectively. There was no statistically significant difference of age among the three groups (P > 0.05). In all the three groups, the majority of the patients belonged to the age group 41–56 years. The three groups were evenly matched with respect to age. This has helped us to judge the clinical significance of our study as the distribution, metabolism, excretion and action of the drug are undoubtedly varied in different age groups. Therefore, clinically insignificant variation in age simply helped to alleviate these confounding factors. All of the three groups were statistically similar with regard to the sex distribution of the patients. Hence, gender was not the confounding factor in the analysis of results.

In this study, all three groups had a majority of patients in the ASA Grade 1. Patients with ASA Grade 3 and Grade 4 were excluded from the study. The groups were similar in terms of ASA grade also. Therefore, our study was conducted mostly on fit patients having no systemic illness, and there was no systemic disease significantly altering the drug metabolism in patients selected for the study.

All patients in control Group C were anxious before induction, while patients in the pregabalin Group A and the clonidine Group B were sedated and showed decrease in anxiety as compared to patients in the control Group C. Preoperative anxiolysis and sedation were higher in oral pregabalin Group A as compared with clonidine Group B. There was statistically significant difference in MBP at time of exsufflation, extubation and in postoperative period between Group A and Group C whereas MBP was significantly lower in Group B when compared with Group A and Group C. Preoperative anxiolysis and sedation were higher in oral pregabalin Group A as compared with clonidine Group B. There was statistically significant difference in MBP at time of exsufflation, extubation and in postoperative period between Group A and Group C whereas MBP was significantly lower in Group B when compared with Group A and Group C.

**DISCUSSION**

The hemodynamic responses to laryngoscopy and laparoscopy, comprising of elevation in HR and rise in systolic and DBP, are well known. It has become imperative to develop a novel technique/drug to prevent these potentially hazardous responses.[8]

The drugs for controlling these hemodynamic responses aim to stabilize HR and blood pressure during laryngoscopy and laparoscopy. Safety of such drugs is also a prime concern.

In the present study, we found that both pregabalin or clonidine are effective in maintaining the hemodynamic stability during laryngoscopy and LC with minimal side effects, with clonidine providing a better hemodynamic stability than Pregabalin.

All patients selected in the study belonged to the age between 18 and 55 years. The mean age of patients in group A, B, and

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**Table 1: Comparison of baseline characteristics between Groups A, B and C**

| Baseline characteristics | A (n=30) | B (n=30) | C (n=30) | P | 95% CI; df |
|--------------------------|----------|----------|----------|---|-----------|
| Age (years)              |          |          |          |   |           |
| 18-30, n (%)             | 6 (20)   | 9 (30)   | 8 (26.67)| 0.906 | Chi-square test=1.027 (df=4) |
| 31-40, n (%)             | 9 (30)   | 9 (30)   | 8 (26.67)| 0.237 | Fisher's exact test (df=2) |
| 41-56, n (%)             | 15 (50)  | 12 (40)  | 14 (46.67)| 0.689 | Fisher's exact test (df=1) |
| Mean±SD                  | 40.87±11.04 | 38.3±11.17 | 39.4±12.4 | 0.739 | Chi-square test=0.111 (df=2) |
| Median (IQR)             | 40.5 (32.75-49.75) | 37.5 (28.5-48.75) | 40 (27.5-50.75) | 0.559 | Fisher's exact test (df=2) |
| Range                    | 23-55    | 21-56    | 18-56    | 0.706 | Chi-square test=0.001 (df=4) |
| Gender                   |          |          |          |   |           |
| Male                     | 9 (30)   | 7 (23.33)| 7 (23.33)| 0.553 | Fisher's exact test (df=1) |
| Female                   | 21 (70)  | 23 (76.67)| 23 (76.67)| 0.792 | Fisher's exact test (df=4) |
| ASA status, n (%)        |          |          |          |   |           |
| I                        | 27 (90)  | 25 (83.33)| 24 (80)  | 0.553 | Fisher’s exact test (df=1) |
| II                       | 3 (10)   | 5 (16.67)| 6 (20)   | 0.630 | Fisher’s exact test (df=2) |
| Ramsay sedation score, n (%) | 0 | 0 | 0 | <0.0001 | Fisher’s exact test (df=4) |

**SD=Standard deviation, IQR=Interquartile range, ASA=American Society of Anaesthesiologists, CI=Confidence interval**
| HR (bpm) | A (n=30) | B (n=30) | C (n=30) | P       | 95% CI | ANOVA; df |
|----------|-----------|-----------|-----------|---------|--------|----------|
| Preoperative |           |           |           |         |        |          |
| Mean±SD  | 78.9±10.58 | 83.43±11.67 | 80.37±10.53 | 0.266   |        | F=1.341; df=87 |
| Median (IQR) | 77.5 (71.25-83.75) | 86.5 (73-93) | 78.5 (72.5-87.75) | A versus B: 0.120 | A versus B: 0.120 | df=58 |
| Range    | 64-113    | 61-104    | 61-113    |         |        |          |
| Premedication |           |           |           |         |        |          |
| Mean±SD  | 82.03±11.23 | 80.73±9.72 | 81.13±11.07 | 0.890   |        | F=0.116; df=87 |
| Median (IQR) | 79.5 (74-85) | 82.5 (71.75-88) | 82 (74-86.75) | A versus B: 0.633 | A versus B: 0.633 | df=58 |
| Range    | 70-120    | 61-98     | 61-120    |         |        |          |
| Induction |           |           |           |         |        |          |
| Mean±SD  | 85.27±11.65 | 83.87±9.58 | 83.73±9.74 | 0.817   |        | F=0.201; df=87 |
| Median (IQR) | 85 (76.25-91.5) | 84 (79.88-87.5) | 83.5 (77.25-90) | A versus B: 0.582 | A versus B: 0.582 | df=58 |
| Range    | 71-120    | 65-102    | 65-102    |         |        |          |
| Laryngoscopy |           |           |           |         |        |          |
| Mean±SD  | 99.77±10.82 | 93.07±9.64 | 100.47±9.53 | 0.008   |        | F=4.995; df=87 |
| Median (IQR) | 98 (95.25-103) | 92.5 (86.5-100) | 99.5 (95.25-106) | A versus B: 0.014 | A versus B: 0.014 | df=58 |
| Range    | 84-130    | 71-112    | 88-130    |         |        |          |
| 1 min    |           |           |           |         |        |          |
| Mean±SD  | 94.47±8.01 | 89.3±7.95 | 91.5±9.54 | 0.018   |        | F=1.172; df=87 |
| Median (IQR) | 96 (90-98.75) | 90 (84-94.75) | 95 (90-97.75) | A versus B: 0.015 | A versus B: 0.015 | df=58 |
| Range    | 82-113    | 74-102    | 81-118    |         |        |          |
| 5 min    |           |           |           |         |        |          |
| Mean±SD  | 88.53±8.29 | 84.47±7.86 | 89.9±8.81 | 0.036   |        | F=3.453; df=87 |
| Median (IQR) | 86.5 (84-91.5) | 86 (75.9-80) | 90 (84-93) | A versus B: 0.538 | A versus B: 0.538 | df=58 |
| Range    | 76-111    | 70-100    | 76-111    |         |        |          |
| 15 min   |           |           |           |         |        |          |
| Mean±SD  | 85.03±7.57 | 81.9±8.15 | 85.83±8.42 | 0.141   |        | F=1.999; df=87 |
| Median (IQR) | 82.5 (80-88.75) | 84 (74.5-88) | 86 (80-89.75) | A versus B: 0.128 | A versus B: 0.128 | df=58 |
| Range    | 75-103    | 68-94     | 71-108    |         |        |          |
| Insufflation |           |           |           |         |        |          |
| Mean±SD  | 99.83±9.88 | 92.6±10.33 | 108.3±10.21 | <0.0001 |        | F=18.012; df=87 |
| Median (IQR) | 98 (93.25-104.75) | 93 (83.5-100.25) | 110.5 (100-116.25) | A versus B: 0.007 | A versus B: 0.007 | df=58 |
| Range    | 84-122    | 74-111    | 89-125    |         |        |          |
| 5 min    |           |           |           |         |        |          |
| Mean±SD  | 96.43±10.81 | 89.27±10.02 | 105.07±10.53 | <0.0001 |        | F=17.168; df=87 |
| Median (IQR) | 94.5 (88-102.25) | 90 (84-97.25) | 105 (97-110) | A versus B: 0.01 | A versus B: 0.01 | df=58 |
| Range    | 82-117    | 70-107    | 87-127    |         |        |          |
| 15 min   |           |           |           |         |        |          |
| Mean±SD  | 93.6±10.32 | 85.6±9.05 | 103.53±8.68 | 0.141   |        | F=1.999; df=87 |
| Median (IQR) | 92 (87-98) | 86 (80.25-91.5) | 103 (97.25-110) | A versus B: 0.128 | A versus B: 0.128 | df=58 |
| Range    | 80-116    | 69-105    | 88-119    |         |        |          |
| 30 min   |           |           |           |         |        |          |
| Mean±SD  | 90.5±9.91 | 83.87±9.05 | 102.1±8.61 | <0.0001 |        | F=30.139; df=87 |
| Median (IQR) | 89.5 (83.25-94.5) | 84 (78.5-88) | 101.5 (96.25-109) | A versus B: 0.008 | A versus B: 0.008 | df=58 |
| Range    | 78-115    | 69-104    | 89-120    |         |        |          |
| 45 min   |           |           |           |         |        |          |
| Mean±SD  | 89.23±9.62 | 82.4±8.29 | 98.97±7.78 | <0.0001 |        | F=28.129; df=87 |
| Median (IQR) | 88 (84-95) | 82 (78.25-86.75) | 98.5 (92.25-103) | A versus B: 0.004 | A versus B: 0.004 | df=58 |
| Range    | 75-108    | 66-98     | 86-117    |         |        |          |

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Table 2: Comparison of systolic blood pressure (mmHg) between Groups A, B and C

| SBP (mmHg) | A (n=30) | B (n=30) | C (n=30) | P | 95% CI; df |
|------------|----------|----------|----------|---|------------|
| Preoperative |          |          |          |   |            |
| Mean±SD    | 123.97±11.77 | 129.3±15.32 | 124.67±11.16 | 0.224 | ANOVA; F=1.518; df=87 |
| Median (IQR)| 124 (114-132) | 129 (121-136) | 125 (116.75-133) | A versus B: 0.136; A versus C: 0.814; B versus C: 0.185 |            |
| Range      | 102-145 | 93-176 | 98-143 |            |            |
| Premedication |          |          |          |   |            |
| Mean±SD    | 123.6±13.82 | 128.67±14.42 | 123.77±13.65 | 0.284 | ANOVA; F=1.274; df=87 |
| Median (IQR)| 126.5 (111-131.5) | 129.5 (120-136.75) | 122.5 (111.75-133.75) | A versus B: 0.17; A versus C: 0.962; B versus C: 0.181 |            |
| Range      | 100-155 | 97-167 | 100-155 |            |            |
| Induction |          |          |          |   |            |
| Mean±SD    | 123.37±13.24 | 121.37±12.92 | 120.57±10.91 | 0.667 | ANOVA; F=0.406; df=87 |
| Median (IQR)| 123 (112-131.25) | 121.5 (111-128.75) | 122.5 (112-126) | A versus B: 0.556; A versus C: 0.375; B versus C: 0.796 |            |
| Range      | 103-160 | 88-150 | 102-145 |            |            |
| Laryngoscopy |          |          |          |   |            |
| Mean±SD    | 142.77±12.44 | 133.27±15.03 | 142.3±15.03 | 0.017 | ANOVA; F=0.255; df=87 |
| Median (IQR)| 141 (136.5-148) | 134.5 (123.5-143) | 140 (131.5-150.75) | A versus B: 0.009; A versus C: 0.896; B versus C: 0.023 |            |
| Range      | 122-180 | 85-161 | 111-180 |            |            |
| 1 min      |          |          |          |   |            |
| Mean±SD    | 138.43±12.89 | 132.97±14.38 | 138.23±14.27 | 0.228 | ANOVA; F=1.5; df=97 |
| Median (IQR)| 136 (130-146) | 134.5 (126-142) | 136 (130-145.25) | A versus B: 0.126; A versus C: 0.954; B versus C: 0.159 |            |
| Range      | 113-176 | 102-164 | 102-176 |            |            |
| 5 min      |          |          |          |   |            |
| Mean±SD    | 130.37±11.27 | 126.63±16.4 | 128.73±13.31 | 0.578 | ANOVA; F=0.55; df=87 |
| Median (IQR)| 130 (123.25-137.25) | 129 (115.25-139.5) | 130.5 (122.5-137.5) | A versus B: 0.309; A versus C: 0.609; B versus C: 0.588 |            |
| Range      | 105-162 | 82-155 | 82-150 |            |            |
| 15 min     |          |          |          |   |            |
| Mean±SD    | 125.03±9.62 | 122.97±14.97 | 125±11.05 | 0.751 | ANOVA; F=0.287; df=87 |
| Median (IQR)| 127 (119.75-132) | 127 (112.5-132) | 127 (115.25-133.5) | A versus B: 0.527; A versus C: 0.990; B versus C: 0.551 |            |
| Range      | 104-138 | 78-144 | 99-143 |            |            |

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The mean baseline pulse rate, SBP, DBP, and MBP were similar in all the groups. The comparability of the baseline characteristics in a randomized controlled trial ensures that the outcome is purely linked to the intervention and is not a chance effect as was seen in our study.

On monitoring the stages of preparation, intubation and surgery, we found that the hemodynamic variability was more pronounced during laryngoscopy and intubation among the control population. They reported a significantly better hemodynamic stabilization with least rise in HR and blood pressures during various procedures involved in the surgery and even at extubation and in the postoperative period as compared to both the control group and pregabalin group. Our findings are in line with various previous studies who compared clonidine and pregabalin or control population and found a significantly better hemodynamic stability with least rise in HR and blood pressures during various procedures involved in the surgery.

Our findings are similar in all the groups. The comparability of the baseline characteristics in a randomized controlled trial ensures that the outcome is purely linked to the intervention and is not a chance effect as was seen in our study.

The time periods at which the HR and BP becomes unavoidable. The rise in the hemodynamic parameters was significantly attenuated in the clonidine group than pregabalin and control group. Clonidine provided better hemodynamic stability with least rise in HR and blood pressures during various procedures involved in the surgery and even at extubation and in the postoperative period as compared to both the control group and pregabalin group. Our findings are in line with various previous studies who compared clonidine and pregabalin or control population and found a significantly better hemodynamic stabilization with Clonidine.[9,10] Even, the time periods at which the HR and BP were significantly different among the intervention groups were mostly similar. Gupta et al.[17] reported hemodynamic variability after laryngoscopy with maximal rise after 1 min of laryngoscopy in the control population. They reported a statistically significant attenuation of HR and BM in the control group than pregabalin and control group. Clonidine provided better hemodynamic stability with least rise in HR and blood pressures during various procedures involved in the surgery and even at extubation and in the postoperative period as compared to both the control group and pregabalin group. Our findings are in line with various previous studies who compared clonidine and pregabalin or control population and found a significantly better hemodynamic stabilization with Clonidine.

### Table 3: Contd...

| SBP (mmHg) | A (n=30) | B (n=30) | C (n=30) | P     | 95% CI; df |
|------------|---------|---------|---------|-------|-----------|
| Median (IQR) | 142.5 (136.25-148.5) | 122.5 (112.75-130) | 164 (147.5-170) | A versus B: <0.0001 | A versus B: 16.786-28.481; df=58 |
| Range      | 129-178 | 97-142  | 138-202 | A versus C: <0.0001 | A versus C: <24.647-11.42, df=58 |
| 5 min      | 143.4±8.7 | 118.6±8.7 | 161.5±15.76 | B versus C: <0.0001 | B versus C: <47.811--33.522, df=58 |
| Median (IQR) | 139.5 (137-150) | 120 (112.5-129.5) | 165 (148-174.75) | <0.0001 | A versus B: 18.729-30.738; df=58 |
| Range      | 132-167 | 81-140  | 122-185 | A versus C: <0.0001 | A versus C: 24.787--11.546; df=58 |
| 15 min     | 141.13±9.59 | 115.93±14.11 | 156.7±14.23 | 0.751 | B versus C: 0.527 |
| Median (IQR) | 141 (134-145.75) | 118 (105.25-125.5) | 156.5 (145.5-166.75) | A versus B: 0.99 | A versus C: 5.322-5.389; df=58 |
| Range      | 127-164 | 81-138  | 129-180 | A versus C: 0.551 | B versus C: 8.834-4.768; df=58 |
| 30 min     | 138.33±9.46 | 116.3±13.1 | 150±13.3 | <0.0001 | A versus B: 16.127-27.94; df=58 |
| Median (IQR) | 138.5 (132.25-142) | 115 (108.5-124) | 151 (142-158) | A versus C: 0.0002 | B versus C: <0.0001 |
| Range      | 120-170 | 88-144  | 111-172 | A versus C: 0.051 | B versus C: <40.523-26.877; df=58 |
| 45 min     | 133.3±10.19 | 114.27±14.93 | 145.33±11.32 | <0.0001 | A versus B: 12.41-25.657; df=58 |
| Median (IQR) | 134 (127.25-138) | 112.5 (106.5-127.25) | 145 (139-155) | A versus C: 0.0001 | B versus C: <0.0001 |
| Range      | 113-165 | 80-139  | 118-166 | A versus C: 0.0002 | B versus C: <37.913-24.22; df=58 |
| Exsufflation | 125.3±11.13 | 113.13±15.02 | 128.1±14.1 | 0.0001 | A versus B: 10.39; df=87 |
| Median (IQR) | 126 (118.5-132) | 110.5 (101.25-125.25) | 127 (118-139.75) | A versus C: 0.0008 | B versus C: <48.564-64; df=58 |
| Range      | 108-162 | 89-139  | 98-154 | A versus C: 0.396 | B versus C: <4.285-7.437; df=58 |
| Extubation  | 118.53±11.04 | 112.97±15.15 | 119.5±11.42 | 0.104 | A versus B: 3.285-19.12; df=58 |
| Median (IQR) | 121.5 (112.25-123.75) | 111 (102.5-123) | 121.5 (112.25-129.5) | A versus C: 0.740 | B versus C: <6.771-4.838; df=58 |
| Range      | 98-148 | 84-142  | 98-136 | A versus C: 0.064 | B versus C: <13.467-0.4; df=58 |
| Postoperative 10 min | 115.4±11.67 | 112.87±14.55 | 115.07±8.23 | 0.66 | A versus B: 4.248-9.381; df=58 |
| Median (IQR) | 116 (105-123.5) | 113 (103.25-122.75) | 114.5 (110-122) | A versus C: 4.852-5.855; df=58 | B versus C: <8.343-3.943; df=58 |
| Range      | 94-139 | 81-144  | 96-127 | A versus C: 0.474 | B versus C: <8.343-3.943; df=58 |

SBP=Systolic blood pressure, SD=Standard deviation, IQR=Interquartile range, CI=Confidence interval
### Table 4: Comparison of diastolic blood pressure (mmHg) between Groups A, B and C

| DBP (mmHg) | A (n=30) | B (n=30) | C (n=30) | P       | 95% CI         |
|------------|----------|----------|----------|---------|---------------|
| Preoperative |          |          |          |         |               |
| Mean±SD    | 77.57±8.19 | 78.87±8.77 | 76.03±7.71 | 0.414   | ANOVA; F=0.89; df=87 |
| Median (IQR)| 78 (72-81) | 77.5 (72.5-85.5) | 74.5 (71.25-80) | A versus B: 0.555 | A versus B: −5.684-3.084; df=58 |
| Range      | 60-96    | 62-96    | 64-97    |         | A versus C: 2.577-5.644; df=58 |
|            |          |          |          |         | B versus C: −1.434-7.101; df=58 |
| Premedication |         |          |          |         |               |
| Mean±SD    | 76.33±9.46 | 78.63±8.74 | 74.83±8.57 | 0.257   | ANOVA; F=1.377; df=87 |
| Median (IQR)| 76.5 (70-82) | 76 (72.25-86.25) | 74 (69.25-78) | A versus B: 0.332 | A versus B: −7.008-2.408; df=58 |
| Range      | 60-102   | 64-97    | 64-104   |         | A versus C: 0.522; df=58 |
|            |          |          |          |         | B versus C: 0.994; df=58 |
| Induction  |          |          |          |         |               |
| Mean±SD    | 79.1±9.93 | 75.2±10.08 | 76.57±9.62 | 0.304   | ANOVA; F=1.205; df=87 |
| Median (IQR)| 77.5 (72.5-83.75) | 73.5 (70-81.5) | 74.5 (71.25-81) | A versus B: 0.136 | A versus B: −1.257-7.584; df=58 |
| Range      | 59-104   | 58-99    | 65-102   |         | A versus C: 0.319; df=58 |
|            |          |          |          |         | B versus C: 0.593; df=58 |
| Laryngoscopy |         |          |          |         |               |
| Mean±SD    | 92.37±8.87 | 85.63±11.72 | 92.9±10.95 | 0.015   | ANOVA; F=4.396; df=87 |
| Median (IQR)| 90 (88-95) | 86 (80-91.5) | 90 (88-99.75) | A versus B: 0.014 | A versus B: 1.361-12.105; df=58 |
| Range      | 80-114   | 49-116   | 66-114   |         | A versus C: 0.836; df=58 |
|            |          |          |          |         | B versus C: 0.016; df=58 |
| 1 min      |          |          |          |         |               |
| Mean±SD    | 86.47±10.23 | 82.5±10.83 | 87.97±10.03 | 0.114   | ANOVA; F=2.226; df=87 |
| Median (IQR)| 85 (80.25-91.75) | 85 (78.5-89) | 88 (84-93.75) | A versus B: 0.150 | A versus B: −1.478-9.411; df=58 |
| Range      | 66-110   | 56-100   | 56-110   |         | A versus C: 0.568; df=58 |
|            |          |          |          |         | B versus C: 0.047; df=58 |
| 5 min      |          |          |          |         |               |
| Mean±SD    | 79.77±9.92 | 76.87±11.82 | 79.47±12.34 | 0.558   | ANOVA; F=0.586; df=87 |
| Median (IQR)| 79 (73.25-84) | 79 (70-85.5) | 81 (76-87) | A versus B: 0.307 | A versus B: −2.738-8.538; df=58 |
| Range      | 62-106   | 42-90    | 42-106   |         | A versus C: 0.917; df=58 |
|            |          |          |          |         | B versus C: 0.408; df=58 |
| 15 min     |          |          |          |         |               |
| Mean±SD    | 78.63±8.58 | 74.47±11.19 | 76.8±10.44 | 0.284   | ANOVA; F=1.275; df=87 |
| Median (IQR)| 79.5 (74.5-83) | 76 (69.5-80.75) | 77.5 (73.25-82.5) | A versus B: 0.111 | A versus B: −3.105-6.772; df=58 |
| Range      | 55-100   | 41-92    | 41-100   |         | A versus C: 0.460; df=58 |
|            |          |          |          |         | B versus C: 0.407; df=58 |
| Insufflation |         |          |          |         |               |
| Mean±SD    | 96.2±7.05 | 73.7±10.61 | 101.43±8.52 | <0.0001 | ANOVA; F=83.187; df=87 |
| Median (IQR)| 97.5 (88.75-99.75) | 76 (69.25-80) | 99 (98-107.75) | A versus B: <0.0001 | A versus B: 17.845-27.155; df=58 |
| Range      | 83-111   | 43-90    | 79-120   |         | A versus C: 0.012; df=58 |
|            |          |          |          |         | B versus C: <0.0001; df=58 |
| 5 min      |          |          |          |         |               |
| Mean±SD    | 95.53±6.04 | 71.2±10.97 | 101.3±8.09 | <0.0001 | ANOVA; F=103.39; df=87 |
| Median (IQR)| 96 (92.25-98.75) | 73 (64.5-77.5) | 102 (94.5-107.75) | A versus B: <0.0001 | A versus B: 19.73-28.937; df=58 |
| Range      | 83-111   | 44-92    | 81-116   |         | A versus C: 0.002; df=58 |
|            |          |          |          |         | B versus C: <0.0001; df=58 |
| 15 min     |          |          |          |         |               |
| Mean±SD    | 92.4±6.09 | 69.13±11.49 | 99.57±7.74 | 0.284   | ANOVA; F=1.275; df=87 |
| Median (IQR)| 93 (89-95.75) | 70 (64.25-75.5) | 98 (95.25-106.75) | A versus B: 0.111 | A versus B: −0.988-9.321; df=58 |
| Range      | 82-107   | 44-90    | 77-114   |         | A versus C: 0.46; df=58 |
|            |          |          |          |         | B versus C: 0.407; df=58 |
| 30 min     |          |          |          |         |               |
| Mean±SD    | 89.53±4.9 | 69.7±10   | 96.87±7.07 | <0.0001 | ANOVA; F=102.104; df=87 |
| Median (IQR)| 90 (87-91) | 70 (62.5-77.5) | 97.5 (93-101.75) | A versus B: <0.0001 | A versus B: 15.73-23.937; df=58 |
| Range      | 80-102   | 47-89    | 75-108   |         | A versus C: <0.0001; df=58 |
|            |          |          |          |         | B versus C: <0.0001; df=58 |
| 45 min     |          |          |          |         |               |
| Mean±SD    | 85.33±5.33 | 68.67±11.87 | 93.93±6.14 | <0.0001 | ANOVA; F=71.747; df=87 |

Contd...
### Table 4: Contd...

| DBP (mmHg) | A (n=30) | B (n=30) | C (n=30) | P        | 95% CI               |
|------------|----------|----------|----------|----------|----------------------|
| Median (IQR) | 85 (83-87) | 72 (60.5-76) | 94.5 (90-97.75) | A versus B: <0.0001 | A versus B: 11.865-21.468; df=58 |
| Range | 75-101 | 42-88 | 76-104 | A versus C: <0.0001 | A versus C: -30.186--20.347; df=58 |

**Exsufflation**

| Mean±SD | 79.63±6.33 | 70.13±10.44 | 83.3±10.9 | <0.0001 | ANOVA; F=10.92; df=58 |
| Median (IQR) | 80.5 (75.25-83) | 71 (62-76.75) | 83 (77-89.5) | A versus B: 0.0001 | A versus B: 5.016-13.984; df=58 |
| Range | 66-92 | 48-92 | 48-102 | A versus C: 0.116 | A versus C: -8.273--0.94; df=58 |
|          |          |          |          | B versus C: <0.0001 | B versus C: -18.683--7.65; df=58 |

**Extubation**

| Mean±SD | 75.17±7.51 | 70.17±10.44 | 76.83±9.44 | <0.0001 | ANOVA; F=4.271; df=58 |
| Median (IQR) | 76.5 (70-80) | 70 (64-78) | 77.5 (70.5-82) | A versus B: 0.037 | A versus B: 0.312-9.688; df=58 |
| Range | 60-90 | 50-90 | 50-95 | A versus C: 0.452 | A versus C: -18.683-7.65; df=58 |
|          |          |          |          | B versus C: 0.011 | B versus C: -11.799-1.534; df=58 |

**Postoperative 10 min**

| Mean±SD | 71.33±9.64 | 69.5±9.88 | 71.93±7.05 | 0.55 | ANOVA; F=0.602; df=58 |
| Median (IQR) | 70.5 (65.25-77.75) | 70 (62-78) | 72.5 (68-76) | A versus B: 0.47 | A versus B: -3.213-6.872; df=58 |
| Range | 54-92 | 50-88 | 55-85 | A versus C: 0.784 | A versus C: -4.965-3.765; df=58 |
|          |          |          |          | B versus C: 0.276 | B versus C: -6.869-2.002; df=58 |

SD=Standard deviation, IQR=Interquartile range, CI=Confidence interval, DBP=Diastolic blood pressure

### Table 5: Comparison of mean arterial pressure (mmHg) between Groups A, B and C

| MAP (mmHg) | A (n=30) | B (n=30) | C (n=30) | P        | 95% CI               |
|------------|----------|----------|----------|----------|----------------------|
| Preoperative |         |          |          |          |                      |
| Mean±SD | 93.03±8.7 | 95.68±10.16 | 92.24±7.97 | 0.306 | ANOVA; F=1.2; df=87 |
| Median (IQR) | 92 (87.333-97.917) | 93.67 (89.917-101.833) | 91.5 (86.333-97.083) | A versus B: 0.283 | A versus B: -7.534-2.245; df=58 |
| Range | 76.67-111.33 | 72.33-116.67 | 76-111.33 | A versus C: 0.715 | A versus C: -3.524-5.102; df=58 |
|          |          |          |          | B versus C: 0.150 | B versus C: -1.287-8.154; df=58 |

| Premedication |         |          |          |          |                      |
| Mean±SD | 92.09±10.13 | 95.31±10.15 | 91.14±9.5 | 0.239 | ANOVA; F=1.453; df=58 |
| Median (IQR) | 93 (84-97.167) | 95.33 (87.417-100.833) | 90.83 (83.75-95.833) | A versus B: 0.223 | A versus B: -8.461-2.016; df=586 |
| Range | 76.67-119 | 75-120.33 | 76.67-121 | A versus C: 0.710 | A versus C: -4.129-6.017; df=58 |
|          |          |          |          | B versus C: 0.105 | B versus C: -0.912-9.245; df=58 |

| Induction |         |          |          |          |                      |
| Mean±SD | 93.86±9.74 | 90.59±10.59 | 91.23±9.34 | 0.403 | ANOVA; F=0.916; df=87 |
| Median (IQR) | 93.33 (86.417-98.667) | 89.33 (84.833-97.167) | 90.67 (83.5-95.75) | A versus B: 0.218 | A versus B: -1.99-8.524; df=58 |
| Range | 76-120 | 68-114 | 80.33-116 | A versus C: 0.291 | A versus C: -2.308-7.553; df=58 |
|          |          |          |          | B versus C: 0.803 | B versus C: -5.804-4.515; df=58 |

| Laryngoscopy |         |          |          |          |                      |
| Mean±SD | 109.17±9.37 | 101.51±12.17 | 109.37±11.37 | 0.009 | ANOVA; F=4.944; df=87 |
| Median (IQR) | 106.67 (104.083-112.5) | 103.57 (94-107.667) | 106.67 (104.167-115.167) | A versus B: 0.008 | A versus B: 2.043-13.268; df=58 |
| Range | 94.67-131.33 | 61-131 | 81-133.33 | A versus C: 0.941 | A versus C: -5.584-5.184; df=58 |
|          |          |          |          | B versus C: 0.012 | B versus C: -13.942-1.769; df=58 |

| 1 min |         |          |          |          |                      |
| Mean±SD | 103.79±9.95 | 99.32±11.45 | 104.72±10.64 | 0.118 | ANOVA; F=2.183; df=87 |

Contd...
Table 5: Contd...

| MAP (mmHg) | A (n=30) | B (n=30) | C (n=30) | P       | 95% CI; df |
|------------|----------|----------|----------|---------|-----------|
|            | 102.33 (97.167-108.667) | 102.67 (93.833-106.333) | 104.33 (100.333-108.583) | A versus B: 0.112 | A versus B: -1.078-10.012; df=58 |
|            | 88.33-132 | 71.33-121.33 | 71.33-132 | A versus C: 0.726 | A versus C: -6.257-4.391; df=58 |
|            |          |          |          | B versus C: 0.063 | B versus C: -11.113-0.313; df=58 |
|            | 5 min    |          |          |         | ANOVA: F=0.636; df=87 |
|            | 96.63±9.33 | 93.46±12.77 | 95.89±11.86 | 0.531 | A versus B: 0.275 |
|            | (88.833-102.167) | (89.5-101.917) | (92.083-101.167) | A versus C: 0.787 |
|            | 82.67-117.33 | 55.33-111 | 55.33-117.33 | B versus C: 0.447 |
|            |          |          |          |         | ANOVA: F=0.636; df=87 |
|            | 94.1±7.95 | 90.63±12.09 | 92.87±9.89 | 0.408 | A versus B: 0.194 |
|            | (90.417-98.083) | (87.583-97.167) | (89-98.083) | A versus C: 0.596 |
|            | 75-112 | 53.33-109.33 | 60.33-112 | B versus C: 0.436 |
|            | Insufflation |          |          |         | ANOVA: F=92.83; df=87 |
|            | 112.03±6.73 | 89.49±10.73 | 121.53±10.11 | <0.0001 | A versus B: <0.0001 |
|            | (107.333-115.5) | (84.917-95.917) | (114.667-129.333) | A versus C: 0.0001 |
|            | 100.33-132 | 61-107.33 | 98.67-147.33 | B versus C: <0.0001 |
|            | 15 min    |          |          |         | ANOVA: F=108.42; df=87 |
|            | 111.49±6.17 | 87.02±11.47 | 121.39±9.49 | <0.0001 | A versus B: <0.0001 |
|            | (107.583-114.667) | (81.917-93.667) | (114.5-128.333) | A versus C: <0.0001 |
|            | 101.33-129.67 | 56.33-108 | 94.67-135.67 | B versus C: <0.0001 |
|            |          |          |          |         | ANOVA: F=92.83; df=87 |
|            | 108.64±6.19 | 84.73±11.86 | 118.61±8.78 | 0.408 | A versus B: 0.194 |
|            | (104.75-111.917) | (78.417-90.667) | (113.583-124) | A versus C: 0.596 |
|            | 97-126 | 56.33-106 | 94.33-136 | B versus C: 0.436 |
|            | 30 min    |          |          |         | ANOVA: F=94.27; df=87 |
|            | 105.8±5.87 | 85.23±10.74 | 114.58±8.17 | 0.0001 | A versus B: <0.0001 |
|            | (103.75-108.25) | (77.333-91.167) | (109.667-120.25) | A versus C: <0.0001 |
|            | 96.33-124.67 | 60.67-107.33 | 92.33-127 | B versus C: <0.0001 |
|            |          |          |          |         | ANOVA: F=70.102; df=87 |
|            | 101.32±6.39 | 83.87±12.57 | 111.07±6.71 | <0.0001 | A versus B: <0.0001 |
|            | (98.167-103.5) | (77-93) | 112.33 (106.667-115.333) | A versus C: <0.0001 |
|            | 88-122.33 | 57.33-105 | 94-121.33 | B versus C: <0.0001 |

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et al.,[10] at all the observation periods, HR and BP of clonidine group was lower than that of pregabalin group.

The successful attenuation of the stress response with clonidine and pregabalin at the major events of laryngoscopy, intubation, insufflation and extubation, minimizes the risk of an adverse cardiac event during the routine surgery of LC especially in elderly and hemodynamically compromised patients. As clonidine showed a better response than pregabalin; it holds a clinical relevance for its use in routine practice as it provided the better efficacy and minimal side effects.

The administration of clonidine must be cautioned for dosage as it shown varied response at different doses (2–5 ug/kg) as shown in different studies.[11-13] Higher dose of clonidine (5 ug/kg) is usually required for potentiation of postoperative analgesia by intrathecal morphine whereas a small oral dose of clonidine decreased the incidence of perioperative myocardial ischemic episodes without affecting hemodynamic stability. Mrinmoy et al. stressed on a dose of 150 ug as a good standard dose for reducing hemodynamic changes during the operation.[3]

Another clinical relevance of the use of clonidine would be the decreased need for isoflurane and antihypertensives such as esmolol during the surgery as clonidine serves with a multipurpose function due to its varied mechanisms of sympathetic antagonist and antihypertensive. In addition, it also helps prevent certain other complication during the surgery such as perioperative shivering by inhibiting cold thermoregulatory response, and nausea/vomiting by increasing gastrointestinal motility by decreasing sympathetic outflow and increasing parasympathetic out-flow from the central nervous system. This antiemetic property needs clarification of the mechanism from the future studies.

The study holds strength in being a randomized controlled trial comparing two drugs at a time and the results hold clinical significance to propose the routine use of clonidine in a common surgery (LC).

The study suffers from the limitation in not comparing the different doses of clonidine. And in the newer setups, conventional 4-port LC is being replaced by 3-port and single port LC; thus, the use of clonidine also needs to be explored in the modified versions of LC which was not done in the current study.

**ConCluSion**

Oral premedication with pregabalin (150 mg) and clonidine (200 mcg) are effective in attenuation of the sympathomimetic response to laryngoscopy and laparoscopy with clonidine providing better hemodynamic stability than Pregabalin.

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**Conflicts of interest**

There are no conflicts of interest.
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