*Original Article*

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# Comparison of Gabapentin and Pregabalin Premedication for Attenuation of Hemodynamic Changes in Elective Laparoscopic Appendicectomy

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**Abstract**

*Introduction:* General anaesthesia is the gold standard anaesthetic technique for laproscopic appendicitis. However, this procedure is not risk free. Carbon dioxide is used to create pneumoperitoneum in laproscopic surgeries causes various hemodynamic changes such as abrupt elevation of arterial pressure, systemic vascular resistance and decreased cardiac output. These changes are well tolerated in healthy patients. There is also an increase in circulatory catecholamines during laryngoscopy and intubation. Many pharmacological techniques were evaluated either in the premedication or during the induction to attenuate the hemodynamic response to pneumoperitoneum such as – deepening the anaesthesia, pretreatment with vasodilators, adrenoceptor blockers, calcium channel blockers and opiods. This study is designed to evaluate the hemodynamic changes associated by laryngoscopy, tracheal intubation and pneumoperitoneum in laparoscopic appendicectomy by premedicating the patients with Gabapentin (900mg) and Pregabalin (150mg).

*Materials and Methods:* The study was carried out as a hospital based double blinded randomized prospective comparative study after obtaining institutional ethics committee approval in the Department of Anaesthesiology, SMVMCH Puducherry. The sample size was calculated as 72 with 36 in each group. Patients scheduled for elective laparoscopic appendicectomy were selected for the study based on predetermined inclusion and exclusion criteria. The study drug, Gabapentin 900mg or Pregabalin 150mg, was sealed in a black covered envelope and was given to the patient with sips of water 1 hour before the induction of anaesthesia by an anaesthetist not involved in study. Anaesthetic and surgical techniques were standardized for all patients. HR, SBP, DBP, MAP, SpO2 were recorded at the following points of time:(i) Prior to induction, (ii) 2-3 minutes after intubation, (iii) Before creating pneumoperitoneum, (iv) After creating pneumoperitoneum, (v) 2 minutes after extubation, (vi) Intra op,every 5 mins till the end of surgery, (vii) Post op, every 10 mins for the 1st 30 minutes and then every 30 minutes till 3 hours, along with Ramsay sedation score.

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*Results:* Both the study groups were comparable in terms of age distribution, gender distribution, BMI distribution, duration of surgery. HR changes, SBP changes, DBP changes, MAP changes between the study groups were not significantly different at various different time intervals during intubation and pneumoperitoneum. Lower sedation scores were noted in Gabapentin group and was found to be statistically significant.

*Discussion:* Stress response with laryngoscopy and intubation, and pneumoperitoneum causes exaggerated hemodynamic response and increased intracranial pressure and manifest as tachycardia, hypertension and dysrhythmias. Haemodynamic changes between the study groups were not significantly different at various different time intervals neither during intubation and pneumoperitoneum nor during the surgery and post operatively. Lower sedation scores were noted in Gabapentin group as compared to that of the Pregabalin group at various different time intervals. Both the drugs showed a significant equal and comparable hemodynamic stability during intubation and subsequently during the course of the surgery.

*Conclusion:* Oral Gabapentin and Pregabalin produced similar attenuation of haemodynamic response to laryngoscopy tracheal intubation and pneumoperitoneum. However, lower sedation scores were noted in Gabapentin group as compared to that of the Pregabalin group.

**Keywords:** Pneumoperitoneum; Hemodynamic changes; Laparoscopic surgeries.

## Introduction

Carbon dioxide is the most common gas used to create pneumoperitoneum in laparoscopic surgeries. Adverse cardiovascular effects of carbon dioxide pneumoperitoneum are abrupt elevation of arterial pressure, systemic vascular resistance, heart rate and decreased cardiac output.[1] These hemodynamic changes are mainly due to increased release of catecholamines, vasopressin, or both.[2,3] While this sympathetic response can normally be tolerated by healthy adults, it can be quite hazardous in patients having compromised cardiovascular function.Various anaesthetic techniques has been tried to blunt these deleterious hemodynamic responses like hypertension, tachycardia and arrhythmias in susceptible individuals.

During carbon dioxide pneumo-peritoneum, various physiological changes occurs on cardiovascular, respiratory and excretory systems. The intra-abdominal pressure and the position of patient placed on the operating table determines the severity of these changes. In cardiovascular system - carbon dioxide pneumo-peritoneum reduces the venous return from lower extremities; but the cardiac preload and vascular resistance are increased. In respiratory system - carbon dioxide insufflation causes hypercapnia, it can be easily monitored and corrected in a ventilated patient. There is 30% decrease in Splanchnic, especially mesenteric and renal blood flow.

Many pharmacological techniques were evaluated either in the premedication or during the induction to attenuate these adverse haemodynamic responses to pneumoperitoneum, such as deepening the anaesthesia, pre-treatment with vasodilators, adrenoceptor blockers, calcium channel blockers and opioids, with variable results.4,5 With adequate adjustments and pharmacological interventions, most of the alterations can be managed safely and prevented.[6]

More recently antiepileptic drugs like Gabapentin and Pregabalin have been used for the treatment of acute postoperative pain and to decrease postoperative opioid requirements. Gabapentin is a structural analogue of the neurotransmitter gamma-aminobutyric acid (GABA).[7] It is used to control neuropathic pain, to treat acute post-operative pain and to reduce post-operative opioid requirements. Gabapentin premedication provided perioperative hemodynamic stability during laparoscopic surgery. Gabapentin 900 mg, the recommended dose, when administered 1–2 h before surgery is generally well tolerated without any serious side effects. Therefore we selected 900 mg as the premedication dose of oral gabapentin for this study.[1]

Pregabalin is a structural analog of gamma amino butyric acid (GABA), and shares some characteristics with its predecessor, gabapentin.[8] Pregabalin is used in treatment of neuropathic, inflammatory pain, and acute post-operative pain.[9] Its mechanism of action is by decreasing the synthesis of neurotransmitter glutamate. The peak plasma concentrations of oral pregabalin is within 1 hour. Patients premedicated with pregabalin were haemodynamically stable perioperatively without prolongation of recovery time and side-effects.[10] The attenuation of haemodynamic response is

effective with a single oral dose of 150 mg pregabalin premedication. Therefore we selected 150 mg as the premedication dose of oral pregabalin for this study.

We therefore designed the study to evaluate the hemodynamic changes associated by laryngoscopy, tracheal intubation and pneumoperitoneum in laparoscopic appendicectomy by premedicating the patients with Gabapentin (900mg) and Pregabalin (150mg) 1 hour before the surgery.

## Materials and Methods

The study was conducted in the department of Anaesthesiology at Sri Manakula Vinayagar Medical College and Hospital, Puducherry between October 2016 to May 2018 in patients scheduled for elective laparoscopic appendicectomy. Written informed consent was obtained from all patients and the study was approved by the Institutional Ethics Committee. It was a double blinded randomized prospective comparative study as per good clinical practice (GCP) guidelines by WHO, conducted on 72 patients in which 36 in Group A(received Gabapentin 900mg) and 36 in Group B(received Pregabalin 150mg) as premedication. Patients of ASA(American Society of Anaesthesiologists) physical status I and II of both gender, aged 18 to 60 years, Hypertensives with controlled hypertension were included in the study. Patients having BMI greater than 30, with renal or cardiac dysfunction, taking beta blockers, antipsycotics and anticonvulsants, pregnant or lactating women, patients who are refusing the procedure were excluded from the study. Eligible patients were randomly allotted into two different study groups randomly using sealed envelope technique.

### *Brief Procedure*

All patients were thoroughly examined preoperatively and routine investigation were carried out. Patient were subsequently assessed for eligibility. Group A received Gabapentin 900mgand Group B received Pregabalin 150mg, as premedication 1 hour before surgery.

The group allocation and randomization were done based on computer generated serial number, using Epi-Info Software. The study drug was sealed in a black covered envelope and was given to the patient with sips of water 1hour before the induction of anaesthesia by an anaesthetist not involved in study. The anaesthesia was administered and observation was done by an experienced anaethetist who has no knowledge of whatever drug the patient has taken as premedication.

On arrival to the operation theatre, monitors were attached and baseline heart rate and systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and SpO2 were recorded. Mean arterial pressure (MAP) was calculated by formula MAP = (SBP+2 × DBP)/3.

The pre-operative level of sedation was assessed by the Ramsay sedation scale:

1. Anxious, agitated or restless;
2. Co-operative, oriented and tranquil;
3. Responds to command;
4. Asleep with brisk response to stimulus;
5. Asleep with sluggish response to stimulus;
6. Asleep with no response.

Anaesthetic and surgical techniques were standardized for all patients. An intravenous line will be started using 18 gauge venflon and the patient will be induced anaesthesia by:

(i) Inj.Glycopyrolate 0.2mg IV

(ii) Inj.Fentanyl 2mcg/kg IV

(iii) Inj.Propofol 2mg/kg IV

(iv) Patient was intubated using the appropriate size endotracheal tube and intubation was facilitated by Inj.Atracurium 0.5mg/kg.

(v) Anaesthesia was maintained by 33% O2 in N2O along with 2-2.5% Sevoflurane and intermediate doses of atracurium were administered as per requirement.

Carbon dioxide was insufflated into the peritoneal cavity to create pneumoperitoneum and intraabdominal pressure was maintained to 15 mm Hg. Ventilation was adjusted to maintain ETCO2 within range of 30-40 mm Hg.

In case of any acute/severe hemodynamic fluctuations the following interventions were done:

(i) If heart rate < 20% of the baseline, a bolus of 0.6mg Atropine was given IV.

(ii) If the mean arterial pressure falls < 20% of the baseline, a bolus of 6mg Ephedrine was given IV.

(iii) If the mean arterial pressure rises > 20% of the baseline, a bolus of 5mg Labetolol wasgiven IV.

At the end of surgery, Ondansetron 4mg was administered intravenously for prophylaxis against nausea and vomiting. Residual neuromuscular

block was reversed by using injection neostigmine (0.05mg/kg) and injection glycopyrolate (0.01mg/kg). Tracheal extubation was done when respiration is adequate.

The patients were transferred to the post-anaesthesia care unit and monitored for at least 3 hours, or until there were no signs of any drug-induced effects such as nausea, vomiting, any respiratory inadequacy or haemodynamic instability in form of hypotension/hypertension or tachycardia/bradycardia. If any side-effects were noted, they were treated accordingly.

Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, SpO2 were recorded at the following points of time:

(i) Prior to induction
(ii) 2-3 minutes after intubation
(iii) Before creating pneumoperitoneum
(iv) After creating pneumoperitoneum
(v) 2 minutes after extubation
(vi) Intra-operative, every 5 mins till the end of surgery.
(vii) Post-operative, every 10 mins for the 1st 30 minutes and then every 30 minutes till 3 hours, along with Ramsay sedation score.

### *Statistical Analysis*

Data was entered into Microsoft Excel data sheet and analyzed using SPSS 21.0 version software. Baseline characteristics were represented in the form of Frequencies and proportions. Chi Square test was applied to test statistical difference in proportions. Continuous variables were represented as mean and standard deviation. Comparison of means was done by independent sample 't' test and Mann Whitney U test was applied to test the statistical difference for the non-parametric data. A p-value of <0.05 was considered as statistically significant.

## Results and Discussion

A total of 72 patients, 36 were received 900mg of Gabapentin (Group A) and 36 received 150mg of Pregabalin (Group B) as premedication. Both the study groups were comparable in terms of demographic and baseline characteristics viz, age distribution, gender, BMI, diagnosis and duration of surgery (Table 1). Haemodynamic changes between the Gabapentin and Pregabalin were not significantly different at various different time intervals during intubation and pneumoperitoneum (Table 2 & 3). Haemodynamic changes between the Gabapentin and Pregabalin were not significantly different at various different time intervals during the surgery and post operatively (Figure 1 & 2). Lower sedation scores were noted in Gabapentin group as compared to that of the Pregabalin group of study participants at various different time intervals (Table 4).

Both the drugs showed a significant equal and comparable hemodynamic stability during intubation and subsequently during the course of the surgery. After a detailed review of available literature it was noted that there is deficiency of established research findings comparing Pregabalin and Gabapentin in attenuation hemodynamic stress response to laryngoscopy, intubation and pneumoperitoneum. There were no studies available to the best of our knowledge, comparing the efficacy of Gabapentin and Pregabalin in attenuation of haemodynamic response to pneumoperitoneum/ laparascopy.

Mahoori A et al compared the effect of gabapentin (900mg) and pregabalin (150 mg) two hours prior to induction of anesthesia and stated that significant increase in heart rate and systolic blood pressure and diastolic arterial pressure was observed in placebo group after tracheal intubation, while statistically significant attenuation of hemodynamic changes was seen in gabapentin and pregabalin groups. No adverse outcome was reported in the study groups.[11] Similarly, Namratha S et al investigated the effects of oral gabapentin and pregabalin observed that when compared to gabapentin and pregabalin, there was a significant increase in HR and MAP in control group after laryngoscopy and tracheal intubation.[12] These findings of the above discussed studies were identical to the observations of the present study.

Namratha S et al demonstrated that Pregabalin being more sedative than gabapentin is better than gabapentin in suppressing the pressor response.12 This observation was similar to the present study result where it was noted that lower sedation scores were seen in Gabapentin group as compared to that of the Pregabalin group of study participants at various different time intervals.

In contrast to the identical effects of Pregabalin and gabapentin noted in the present study Waikar C et al evaluated the effect of clonidine 200 µg and gabapentin 900 mg and pregabalin 150 mg in attenuation of the hemodynamic response, reported that mean arterial pressure was well attenuated by pregabalin than others, and mean

**Table 1:** Demographic and Baseline characteristics of study patient in both groups.

| S. No. | Variable | | Group A Gabapentin (n=36) | Group B Pregabalin (n=36) | Total (n=72) | p-Value |
|---|---|---|---|---|---|---|
| 1 | Age in years | | | | | |
| | | 15-30 | 19 | 18 | 37 | 0.863 |
| | | 31-45 | 9 | 11 | 20 | |
| | | 46-60 | 8 | 7 | 15 | |
| 2 | Gender | | | | | |
| | | Male | 21 | 20 | 41 | 0.812 |
| | | Female | 15 | 16 | 31 | |
| 3 | BMI | | | | | |
| | | Underweight | 1 | 4 | 5 | 0.534 |
| | | Normal | 29 | 25 | 54 | |
| | | Overweight | 5 | 6 | 11 | |
| | | Obese | 1 | 1 | 2 | |
| 4 | Diagnosis | | | | | |
| | | Acute Appendicitis | 25 | 27 | 52 | 0.568 |
| | | Sub acute appendicitis | 10 | 9 | 19 | |
| | | Chronic appendicitis | 1 | 0 | 1 | |
| 5 | Duration of Surgery (in mins) | | 60.56±20.76 | 60.69±28.3 | | 0.981 |

**Table 2:** Distribution of study groups based on heart rate changes at various time intervals

| Time Interval | Group A Gabapentin (n=36) | | Group B Pregabalin (n=36) | | p value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Baseline | 83.92 | 15.9 | 81.39 | 13.9 | 0.476 |
| 2-3 mins after intubation | 90.39 | 16.3 | 88.14 | 14.9 | 0.544 |
| Before pneumoperitoneum | 89.9 | 16.3 | 82.3 | 14.2 | 0.038 |
| After Pneumoperitoneum | 91.92 | 19.2 | 85.5 | 16.7 | 0.135 |
| 2 mins after extubation | 105.4 | 17.3 | 102.3 | 18.8 | 0.468 |

**Table 3:** Distribution of study groups based on MAP changes at various time intervals.

| Time Interval | Group A Gabapentin (n=36) | | Group B Pregabalin (n=36) | | p value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Baseline | 91.86 | 14.3 | 94.7 | 13.6 | 0.392 |
| 2-3 mins after intubation | 89.1 | 18.5 | 84.3 | 14.4 | 0.226 |
| Before pneumoperitoneum | 83.5 | 11.9 | 77.4 | 11.6 | 0.032 |
| After Pneumoperitoneum | 91.1 | 13.4 | 88.3 | 15.3 | 0.406 |
| 2 mins after extubation | 100.8 | 13.6 | 104.6 | 12.8 | 0.222 |

**Table 4:** Distribution of study groups based on sedation score at various time intervals.

| Time interval (in mins) | Sedation Score | Study group | | Total n (%) | p value* |
|---|---|---|---|---|---|
| | | Group A Gabapentin n (%) | Group B Pregabalin n (%) | | |
| Pre Surgery | 2 | 36(100.0) | 36(100.0) | 72(100.0) | NA |
| 10 | 3 | 36(100.0) | 36(100.0) | 72(100.0) | NA |
| 20 | 3 | 36(100.0) | 36(100.0) | 72(100.0) | NA |
| 30 | 2 | 3(8.3) | 0(0.0) | 3(4.2) | 0.239 |
| | 3 | 33(91.7) | 36(100.0) | 69(95.8) | |
| 60 | 2 | 13(36.1) | 0(0.0) | 13(18.1) | <0.001 |
| | 3 | 23(63.9) | 36(100.0) | 59(81.9) | |
| 90 | 2 | 28(77.8) | 1(2.8) | 29(40.3) | <0.001 |
| | 3 | 8(22.2) | 35(97.2) | 43(59.7) | |
| 120 | 2 | 35(97.2) | 2(5.6) | 37(51.4) | <0.001 |
| | 3 | 1(2.8) | 34(94.4) | 35(48.6) | |
| 150 | 2 | 35(97.2) | 7(19.4) | 42(58.3) | <0.001 |
| | 3 | 1(2.8) | 29(80.6) | 30(41.7) | |
| 180 | 2 | 35(97.2) | 7(19.4) | 42(58.3) | <0.001 |
| | 3 | 1(2.8) | 29(80.6) | 30(41.7) | |
| Total | | 36(100.0) | 36(100.0) | 72(100.0) | |

heart rate following laryngoscopy and intubation was attenuated by clonidine group significantly.[13]

Bhagat NM et al compared the efficacy of oral premedication with pregabalin versus clonidine on stress response and hemodynamic stability during laryngoscopy in 60 adult patients aged 18-60 years. The study findings documented that Perioperative sedation levels were higher with pregabalin than with clonidine, without prolongation of recovery time. Statistically significant attenuation of mean arterial pressure and heart rate to laryngoscopy and laparoscopy was observed in the premedicated groups. The visual analogue scale scores of both the pregabalin and the clonidine group were significantly lower than that in the control group at 1, 4, and 8 h after surgery.[14] This haemodynamic attenuation by Pregabalin in the above study was similar to that of the present study findings among the Pregabalin group. Likewise, in a study by Gupta K et al it was observed in the study that Pregabalin and clonidine proved to have sedative and anxiolytic effects as oral premedicants and decreased the need of intraoperative analgesic drug requirement during laparascopic cholecystectomy.[15]

Saxena A et al evaluated the effectiveness of pregabalin as a premedication on the arterial pressorresponse to laryngoscopy and on hemodynamic variables and revealed that Pregabalin 75 mg at night and 150 or 300 mg 1 h before surgery adequately attenuates pressor response to laryngoscopy andintubation. Patients' hemodynamic variables were more stable in pregabalin groups as compared to control group (diazepam)during the intra-operative period.16 Chakraborty R et al evaluated the efficacy of preoperative 150 mg of oral pregabalin in attenuating haemodynamic response to laryngoscopy and endotracheal intubation and reported significantly less increase in systolic, diastolic and mean blood pressure in pregabalin groupof patients following intubation when compared to controls (p value = 0.02, 0.03, 0.02 respectively). Preoperative & post-operative sedation scores were relatively higher after pregabalin premedication.[17]

These findings by the above discussed research works were similar to the effects of Pregabalin observed in the present study. In addition, during laryngoscopyand intubation there was significant attenuation of SBP, DBP and MBP in Prebagalin administration as compared to placebo group as reported by Bhandari G et al in their study.[18] The mean arterial pressure was attenuated with oral pregabalin to statistically significant value (P<0.007). The requirement of analgesic drug was reduced with no postoperative respiratory depression, nausea, or vomiting and hemodynamic parameters remained stabilized perioperatively, in the study by Gupta K et al.[19]

Gabapentin also produced a haemodynamic attenuation effect to pneumoperitoneum/ laparasocopy in the present study, similar observations were noted in Prakash R et al study where the effect of oral clonidine and gabapentin premedication on intraoperative haemodynamic stability on 90 patients aged between 20-60 years was studied and noted that both clonidine and gabapentin group had significantly lower HR and BP changes than placebo group (P<0.05) during pneumoperitoneum.[20]

Bhandari G et al evaluated effects of gabapentin on arterial pressure and heart rate at induction of anaesthesia and attracheal intubation and reported that Pre medication with 900 mg gabapentin, 2 hours before induction of anaesthesia attenuatesthe tachycardia associated with laryngoscopy and intubation but not the pressor response completely.[18]

Also, Neogi M et al investigated the efficacy of gabapentin premedication and stated that mean arterial pressure in patients of group Gabapentin were significantly lower (P < 0.05) after tracheal intubation and pneumoperitoneum and remained lower, as compared to group placebo, throughout the pneumoperitoneum.[21] Similarly, heart rate in Gabapentin significantly lower (P < 0.05) after tracheal intubation and pneumoperitoneum and remained lower, in comparison to group palcebo, throughout the peumoperitoneum. These observations of the above research works were similar to that of the findings of the present study.

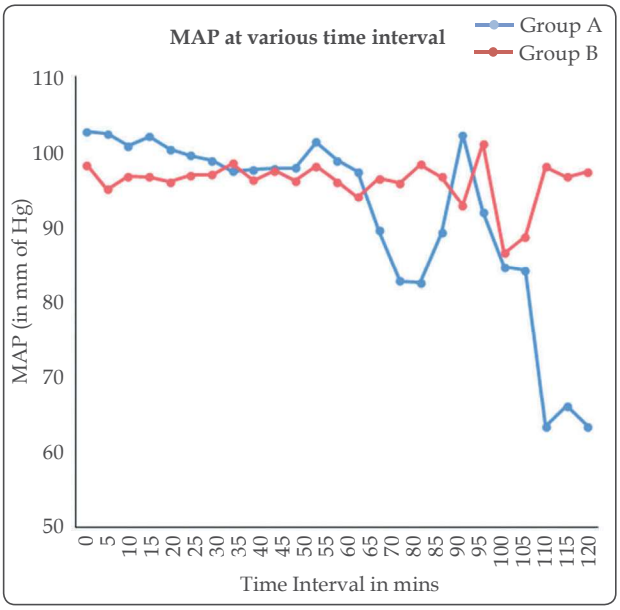


**Fig. 1:** Distribution of study groups based on HR at various time intervals during surgery.

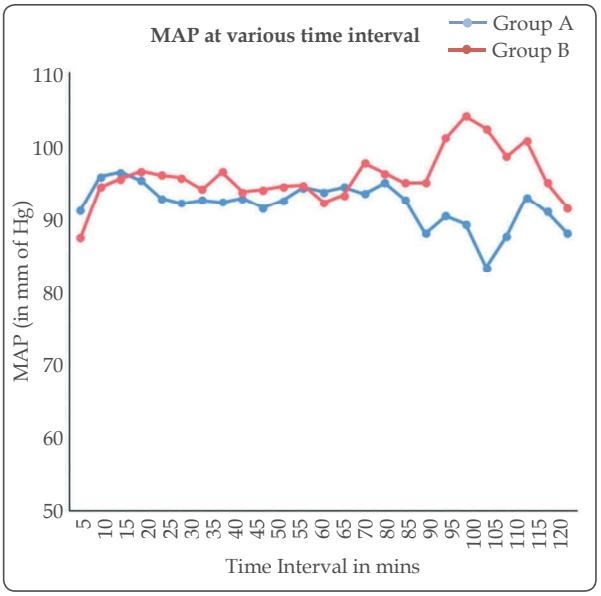


**Fig. 2:** Distribution of study groups based on MAP at various time intervals during surgery.

## Conclusion:

Oral Pergabalin and Gabapentin produced similar attenuation of haemodynamic response to laryngoscopy and intubation. However, lower sedation scores were noted in Gabapentin group as compared to that of the Pregabalin group of study participants at various different time intervals.

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