Comparision of Different Doses of Pregabalin V/S Placebo as Pre-Anesthetic Medication in Patients Undergoing Laparoscopic Cholecystectomy: A Randomized Double Blind Control Study

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ABSTRACT

Introduction: Heart rate and blood pressure rise during laryngoscopy and tracheal intubation is common. Although this reaction is usually brief and has little implications in the majority of cases, it can have catastrophic consequences in those who have underlying abnormalities such as coronary artery disease, reactive airways, or intracranial neuropathology, and thus should be prevented. Study aimed to compare the effects of two different doses of oral pregabalin v/s placebo on attenuation of pressor response during direct laryngoscopy and intubation.

Material and methods: 90 patients of ASA class 1 and 2 of age between 18 to 50 years were selected in the study and divided them into three groups
group 1 was control group,
group 2 was 75mg pregabalin group
group 3 was 150mg pregabalin group.
All the groups received drug 1 hour prior to intubation.

Result: This attenuation of hemodynamic response observed in our study was however found to be dose dependent, as depicted by comparison of two different doses of pregabalin used as premedication. On comparison of pregabalin in doses 75 mg and 150 mg it was found that higher dose, i.e. 150 mg was better in attenuating the pressor response to laryngoscopy.

Conclusion: We concluded that however pregabalin is very effective in attenuating the cardiovascular response with laryngoscopy & intubation, but the response is dose dependent. Oral pregabalin in doses of 150mg given as premedication 1 hour prior to surgery attenuates the cardiovascular response with laryngoscopy and intubation significantly better than oral pregabalin 75 mg or placebo group.

Keywords: Pregabalin V/S Placebo Dose, Pre-Anesthetic Medication, Laparoscopic Cholecystectomy

INTRODUCTION

An ideal premedication drug should relieve anxiety, produce amnesia and sedation, decrease secretions, prevent nausea and vomiting, have dose sparing effect on the anesthetic drugs and suppress presser response to laryngoscopy and intubation[1]. Heart rate and blood pressure rise during laryngoscopy and tracheal intubation is common[2]

A reflex sympathetic reaction to the mechanical stimulation of the larynx and trachea is thought to be the mechanism of cardiovascular response to intubation. It has been shown that laryngoscopy with or without tracheal intubation causes a significant increase in circulating catecholamines[3,4]

Although this reaction is usually brief and has little implications in the majority of cases, it can have catastrophic consequences in those who have underlying abnormalities such as coronary artery disease, reactive airways, or intracranial neuropathology[5,6,7,8]

In patients undergoing surgery requiring general anesthesia, endotracheal intubation is regarded the gold standard. The pressor reaction is a rise in blood pressure and heart rate caused by direct laryngoscopy and intubation. Both sympathetic and parasympathetic nervous system mediate cardiovascular responses to laryngoscopy and endotracheal intubation[9,10,11]

Aim:

To study and compare the effects of two different doses of oral pregabalin v/s placebo on attenuation of pressor response during direct laryngoscopy and intubation.

Objectives:

1. To study hemodynamic parameter which includes Systolic blood pressure(SBP), Diastolic blood pressure (DBP), Mean arterial blood pressure (MAP) and Heart rate (HR).
2. To observe and record side effects of pregabalin if any.

MATERIAL AND METHODS

Place of Study: After obtaining approval of the institutional Ethical Committee and informed consent of the patients, this randomized double blind placebo controlled study will be conducted in the Department of Anaesthesiology, Rohilkhand medical college and hospital. Patients selected for study will be posted for elective laparoscopic cholecystectomy under general anaesthesia.

Type of Study: This is prospective randomized double blind controlled study.

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Study Duration: 1st October 2019- 30th September 2020

Subjects: Ninety patients of either sex and American society of anesthesiology (ASA) I & II physical status, aged 18- 50 years will be selected and scheduled to undergo elective laparoscopic cholecystectomy were enrolled in the study.

Inclusion Criteria:

- American Society of Anaesthesiologists (ASA) physical status I and II
- Age18 to 50 years
- Modified Mallampati classes I, II and III
- Weight 50-90kg
- Either of sexes

Exclusion Criteria:

- Patients with pre-existing cardiac disease, asthma, and severe renal or hepatic dysfunction.
- Anticipated difficult intubation and patients with morbid obesity.
- Patients having history of taking of antidepressants drugs.
- Low pulmonary compliance or high airway resistance e.g. chronic bronchitis, bronchial asthma, interstitial disease
- History of ischemic heart disease
- Known drug allergy
- Chronic renal failure
- Alcohol or drug abuse
- Chronic analgesic abuse
- Already taking pregabalin, gabapentin, sedatives or antidepressant drugs
- Known neurological disease

Method

A similar size ninety opaque envelopes divided into three groups A, B, C of thirty each were taken. A staff nurse separated the capsules of pregabalin 75 mg, pregabalin 150 mg & placebo into three equal groups of thirty each and load them in such a way that either group of envelopes contain one of the study drug.

Group A: patients received oral placebo in the form of oral multivitamin capsules with sip of water 60 min before surgery

Group B: patients received pregabalin 75 mg orally with sip of water 60 min before surgery

Group C: patients received pregabalin 150 mg orally with sip of water 60 min before surgery

Procedure

All the patients were assessed day before surgery and general information regarding the study and consent was explained to them.

Patients were randomly allocated and provided either envelope containing formulations by another staff nurse in preoperative room 60 minutes prior to surgery.

After arrival in the operating room, intravenous access was secured with eighteen gauge(18 G) intravenous cannula in a non dominant hand peripheral vein and a Ringer lactate solution was started at 6ml/kg. Continuous monitoring of heart rate (HR), non invasive blood pressure (NIBP), electrocardiogram (ECG), Pulse oxymeter (SpO2) was carried out using multipara monitor.

A uniform anaesthetic technique was used in all patient of each group.

Patients were premedicated with injection Midazolam (1.0 mg), inj Glycopyrrolate (0.2mg). After 3 minute of preoxygenation, patients were induced with inj Propofol 2mg/kg or in a dose sufficient to loss of verbal commands and relaxed with injection Vecuronium (0.1 mg/kg) to facilitate endotracheal intubation. After 3 minute, endotracheal intubation was done with appropriate size of ET tube and checked for proper placement by 5 point auscultation until no audible leak present after which cuff was inflated.

Following endotracheal intubation, a nasogastric tube (14 F) was placed.

The duration of laryngoscopy and intubation was limited to minimum possible time & tried upto 15 seconds for all patients.

Maintenance of anesthesia was carried out using 67% N_2O in 33% 02 and isoflurane 0.75% using controlled ventilation. Supplemental neuromuscular blockade was achieved with vecuronium (0.01-0.02mg/kg).

An anesthetist, who was blinded to drugs used in each group, will do monitored vital parameters. Heart rate (HR) and Non invasive Systolic blood pressure (NIBP) (mm Hg), diastolic blood pressure (DBP) (mm Hg), mean arterial pressure (MAP) (mmHg) was recorded before and 60 minute after administration of the study drug, immediately after intubation & cuff inflation (0 min) and 2, 4, 6, 8, 10,20, and 30 min after intubation.

At the end of surgery, residual neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01mg/kg intravenously.

RESULT

Table-1 and graph-1 include comparison of variation in heart rate across time periods .The difference in baseline mean heart rate values are not statistically significant in all 3 groups. During laryngoscopy and intubation, group A compared with group B (121.37±2.83,106.87±2.78 p = 0.0001) & group A with group C (121.37 ±2.83,93.03±3.10 p = 0.0001), the difference was statistically significant. Also on comparing group B with group C (106.87±2.78, 93.03±3.10, p = 0.0001), data was statistically significant.

Whole time in the study duration there was statistically significant difference in mean heart rate when group A was compared with group B and group C. when group B compared to group C - the difference was significant.

Baseline mean systolic blood pressure difference between all 3 group is not statistically significant . During laryngoscopy and intubation, when group A compared with group B (149.43 ± 8.08, 140.23 ± 2.65, p = 0.01) & group A with group C (149.43 ± 8.08, 136.07 ± 3.30, p = 0.0001), difference was statistically significant. Also on comparing group B with group C (140.23 ± 2.65, 136.07 ± 3.30, p = 0.001), data was significant. whole time during study there was statistically

Time Interval	Group A *n=30* (Mean ± SD)	Group B *n=30* (Mean ± SD)	Group C *n=30* (Mean ± SD)	p-value		
				Between group A and B	Between group A and C	Between group B and C
Baseline	80.17±7.46	78.97±2.69	82.70±4.08	0.41	0.10	0.10
60 minute after drug administration	79.23±6.33	77.00±3.10	82.90±3.08	0.08	0.06	0.07
During D/L	121.37±2.83	106.87±2.78	93.03±3.10	0.0001	0.0001	0.0001
2 minute	117.03±3.29	106.07±2.87	90.80±3.66	0.0001	0.0001	0.0001
4 minute	116.37±3.24	101.90±3.28	88.50±3.22	0.0001	0.0001	0.0001
6 minute	111.13±2.31	99.83±2.72	88.37±2.96	0.0001	0.0001	0.0001
8 minute	104.63±2.37	97.47±2.05	86.10±2.89	0.0001	0.0001	0.0001
10 minute	100.20±2.10	95.20±2.81	84.53±3.30	0.0001	0.0001	0.0001
20 minute	96.10±1.97	89.43±2.78	83.67±2.70	0.0001	0.0001	0.0001
30 minute	84.43±3.26	83.07±2.72	76.40±3.09	0.0833	0.0001	0.0001

Table-1:

Systolic Blood Pressure (mm Hg)	Group A *n=30* (Mean ±SD)	Group B *n=30* (Mean ±SD)	Group C *n=30* (Mean ±SD)	p-value		
				Between group A and B	Between group A and C	Between group B and C
Baseline	121.93±9.74	124.63±5.91	123.33±5.62	0.19	0.49	0.38
60 minute after drug admin	122.33±9.26	122.87±5.70	120.80±6.32	0.78	0.45	0.18
During D/L	149.43±8.08	140.23±2.65	136.07±3.30	0.0001	0.0001	0.0001
2 minute	139.40±5.59	138.17±3.45	133.20±2.96	0.03	0.0001	0.0001
4 minute	138.73±4.94	137.43±2.49	132.13±2.64	0.02	0.0001	0.0001
6 minute	135.57±5.00	135.73±3.31	130.70±3.39	0.87	0.0001	0.0001
8 minute	133.67±5.04	130.50±3.04	129.00±7.34	0.0004	0.0001	0.0001
10 minute	134.73±5.63	130.07±2.86	127.27±2.24	0.0001	0.0001	0.0001
20 minute	125.37±4.87	128.43±3.40	125.10±3.81	0.0001	0.81	0.07
30 minute	122.17±5.01	127.30±3.47	118.00±2.62	0.005	0.0003	0.04

Table-2:

Diastolic Blood Pressure (mm Hg)	Group A *n=30* (Mean ±SD)	Group B *n=30* (Mean ±SD)	Group C *n=30* (Mean ±SD)	p-value		
				Between group A and B	Between group A and C	Between group B and C
Baseline	71.20±7.57	69.70±4.91	71.87±4.75	0.36	0.68	0.08
60 minute after drug admin	69.70±7.06	69.73±5.60	70.27±5.85	0.98	0.73	0.71
During D/L	93.50±6.62	86.10±5.45	76.23±7.38	0.0001	0.0001	0.0001
2 minute	92.80±5.34	83.40±6.00	74.30±7.74	0.0001	0.0001	0.0001
4 minute	90.87±5.58	80.73±6.12	73.17±5.70	0.0001	0.0001	0.0001
6 minute	87.27±4.68	78.57±6.35	72.40±5.51	0.0001	0.0001	0.0001
8 minute	84.27±5.83	76.73±7.47	71.20±7.37	0.0001	0.0001	0.0001
10 minute	81.50±5.64	74.87±6.73	69.93±6.16	0.0001	0.0001	0.0001
20 minute	75.83±6.82	73.50±6.96	68.27±6.22	0.0001	0.0001	0.0001
30 minute	76.60±5.96	69.73±5.91	66.90±4.89	0.04	0.03	0.04

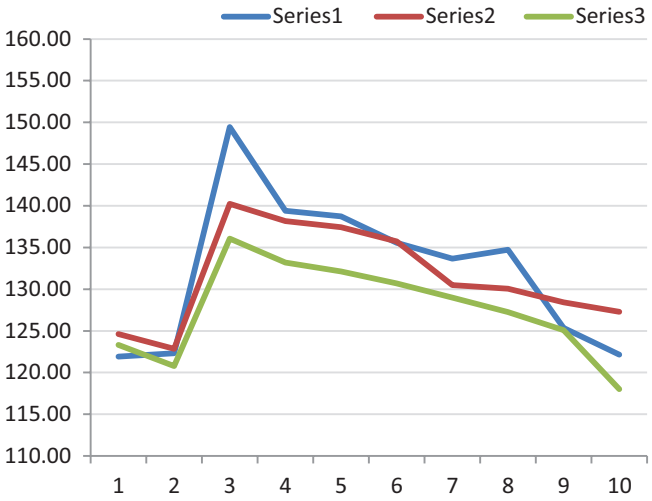
Table-3:

significant difference was present in mean systolic blood pressure when group A was compared with group B and C, except 6 minute after intubation between group A and B. Data was statically significant B and C are compared.

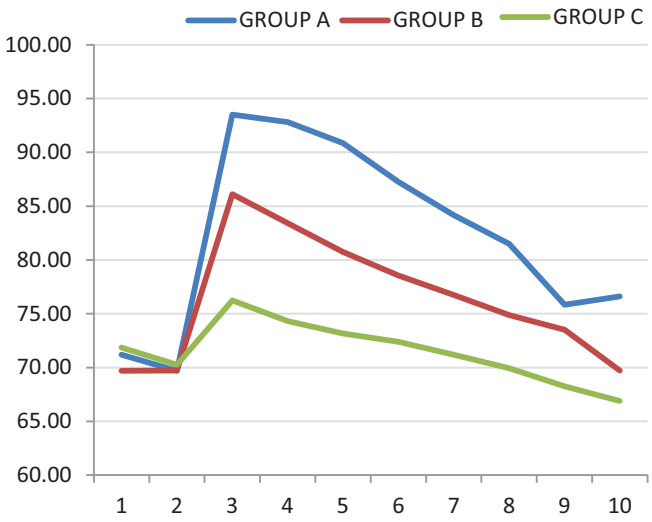
Table3 and graph-3 include comparison of change in diastolic blood pressure. There is no statically significant difference in baseline values of group A B and C. During laryngoscopy and intubation group A compared with group B (93.50 ± 6.62, 86.10 ± 5.45, p = 0.0001) & group A with group C (93.50 ± 6.62, 76.27 ± 7.38, p = 0.0001), was found to be statistically significant. There was also statistically significant difference found when group B compared with group C (86.10 ± 5.45, 76.27 ± 7.38, p = 0.0001). Throughout the study period there was statistically significant difference in mean diastolic blood pressure when group B was compared with group C. When group A was compared with group B, there was statistically significant difference in mean diastolic blood pressure. Also between group A and group C, throughout the study period there was statistically significant difference in mean diastolic blood pressure value.

Mean Arterial Pressure (mm Hg)	Group A n=30 (Mean ±SD)	Group B n=30 (Mean ±SD)	Group C n=30 (Mean ±SD)	p-value		
				Between group A and B	Between group A and C	Between group B and C
Baseline	87.94±6.54	87.83±3.93	88.85±3.45	0.93	0.50	0.28
60 minute after drug admin	87.07±6.52	87.27±4.12	86.94±4.16	0.88	0.92	0.76
During D/L	111.96±5.03	103.96±3.94	95.98±4.94	0.0001	0.0001	0.0001
2 minute	108.18±4.57	101.47±4.21	93.74±5.24	0.0001	0.0001	0.0001
4 minute	106.66±4.20	99.44±4.25	92.63±4.24	0.0001	0.0001	0.0001
6 minute	103.21±3.20	97.43±4.31	91.64±3.98	0.0001	0.0001	0.0001
8 minute	100.50±4.62	94.48±5.11	90.27±6.01	0.0001	0.0001	0.0001
10 minute	99.07±4.00	93.08±4.57	88.85±4.36	0.0001	0.0001	0.0001
20 minute	92.18±4.60	91.63±4.75	87.02±4.60	0.007	0.0001	0.0001
30 minute	91.64±4.28	88.73±3.72	80.16±3.54	0.0001	0.0003	0.0001

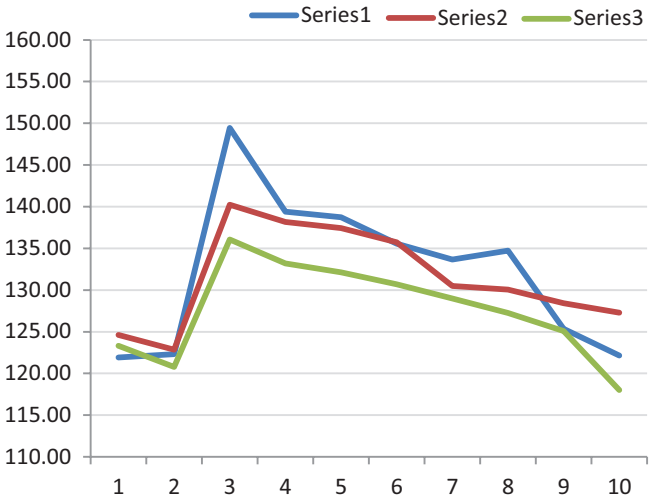
Table-4:



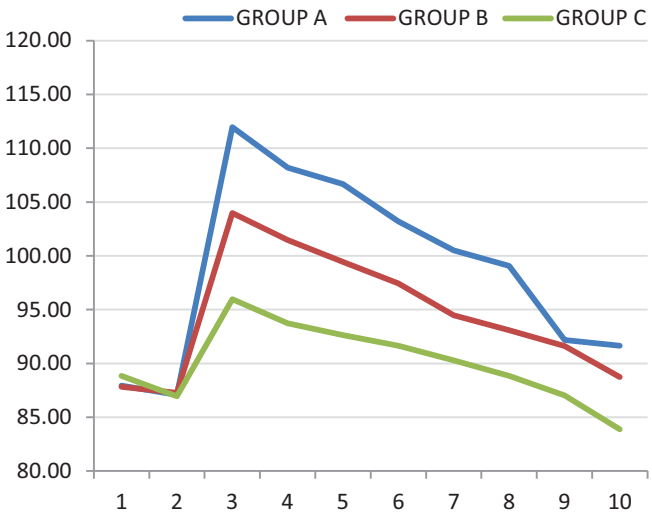
Graph-1:



Graph-3:



Graph-2:



Graph-4:

Table-4 and graph-4 shows Inter-group comparison of change in mean arterial pressure across time periods among the groups. We can see the difference in baseline mean arterial pressure values are not statistically significant among the groups. During laryngoscopy and intubation, when group A compared with group B (111.96 ± 6.52, 103.96 ± 3.94, p = 0.01) & group A with group C (111.96 ± 6.52, 95.98 ± 4.94, p = 0.0001), it was found to be statistically significant. There was also statistically significant difference found when group B compared with group C (103.96 ± 3.94, 95.98 ± 4.94, p = 0.0001).Throughout the study period there was statistically significant difference in mean arterial pressure when group B was compared with group C. When group A was compared

with group B, there was statistically significant difference in mean arterial pressure. Also between group A and group C, throughout the study period there was statistically significant difference in mean arterial pressure value.

DISCUSSION

In our study we found out that there was no significant change in the baseline heart rate (p value 0.41,0.10,0.10) systolic blood pressure (p value 0.19,0.49,0.38) , diastolic blood pressure (p value 0.36,0.68,0.08) and mean blood pressure(0.93,0.50,0.28) between placebo, pregabalin 75mg group and pregabalin 150 mg group respectively. There was also no significant change present in heart rate (p value 0.08,0.06,0.07) systolic blood pressure(p value- 0.78,0.45,0.18), diastolic blood pressure(p value-0.98,0.73,0.71), and mean arterial blood pressure (p value-(0.88,0.92,0.76) between placebo, pregabalin 75mg group and pregabalin 150 mg group respectively after 60minute of drug administration (Table 3,4,5, and 6). This was similar to study done by Rastogi Bhawana and colleagues[12] and Khalida Parveen and colleagues[13].

There was significant reduction in change in hemodynamic response (heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure) in both 75mg pregabalin group and 150mg pregabalin group when compared to placebo at different time interval from direct laryngoscopy to 20minute. p value was statically significant (p=0.001) (Table3,4,5, and 6). At 30 minute change in heart rate (pvalue-0.08) and change in systolic blood pressure (pvalue-0.005), was insignificant between placebo group and 75mg group , but heart rate (pvalue-0.001) and systolic blood pressure(pvalue-0.0003) was statically significant even at 30 minutes on comparing 150mg group with placebo and 75mg group. Probable reason for this was higher dose of pregabalin.

Also when heart rate and systolic blood pressure in between 75mg pregabalin group and 150mg pregabalin was compared , results were significant.(p value-0.001) This shows 150mg pregabalin blunts hemodynamic response better than 75mg pregabalin.

A similar result by Ayya Syama Sundar et al[14]. He too showed that premedication with 150 mg of oral pregabalin safely attenuates increase in arterial blood pressure in response to laryngoscopy and intubation.

In a study done by Eren[15] and colleagues similar results were found. They used pregabalin to know its effectiveness in blunting the hemodynamic response to intubation in lumbar surgeries, among 50 ASA grade I adult patients undergoing elective lumbar disc surgery under general anaesthesia.

CONCLUSION

The cardiovascular response to laryngoscopy and intubation was significantly attenuated when pregabalin was used as premedication compared to control group. This attenuation of hemodynamic response observed in our study was however found to be dose dependent, as depicted by comparison of two different doses of pregabalin used as premedication. On comparison of pregabalin in doses 75 mg and 150 mg it was found that higher dose, i.e. 150 mg was better in attenuating the pressor response to laryngoscopy. Our study shows that Pregabalin can recommended along with other premedication to control and attenuate the hemodynamic response to laryngoscopy and intubation. This should be further evaluated for response and safety profile in high risk patients, hypertensive patient and in patients with history of ischemic heart disease, in whom increased hemodynamic parameter has been found to be associated with detrimental outcome.

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