Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2016/433

Original Article

Effect of Pregabalin Premedication on the Laryngoscopic Response and Intra-operative Hemodynamic Variables in Laparoscopic Cholecystectomy: A Randomized Comparison of Two Doses

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Abstract

Background: Pre-operative medication has a vital role in anesthesia. Pregabalin is a newer drug of gabapentenoid class and is 6 times more potent than gabapentin. It has anxiolytic, sedative, antiallodynic, antihyperalgesic, antinociceptive, and antisecretory properties. This study was designed to know the effectivity of pregabalin as a premedication on the arterial pressor response to laryngoscopy and on hemodynamic variables.

Materials and Methods: This study was conducted on 90 patients of ASA Grade I and II of age group 20-60 years, undergoing laparoscopic cholecystectomy under general anesthesia. They were allocated to one of the three groups of 30 patients each. Group I received tablet diazepam 10 mg HS and 5 mg 1 h before surgery, Group II received capsule pregabalin 75 mg HS and 150 mg 1 h before surgery, and Group III received capsule pregabalin 75 mg HS and 300 mg 1 h before surgery. General anesthesia was induced and maintained by using standard technique. Level of sedation, heart rate, systolic, diastolic, and mean blood pressures (0, 1, 3, 5, 10, 15 min, and intraoperatively every 15 min) were recorded.

Results: Mean age, weight and sex distribution, and duration of laryngoscopy in all the three groups were comparable. Pregabalin 75 mg at night and 150 or 300 mg 1 h before surgery adequately attenuates pressor response to laryngoscopy and intubation. Patients' hemodynamic variables were more stable in pregabalin groups as compared to control group (diazepam) during the intra-operative period.

Conclusion: Oral pregabalin is more effective in blunting the cardiovascular response to laryngoscopy as compared to diazepam, when administered as premedication. Both pregabalin 150 mg and 300 mg were equally effective in diminishing the cardiovascular response to laryngoscopy and reducing the intra-operative hemodynamic perturbations.

Key words: Cardiovascular response to laryngoscopy, Intra-operative hemodynamic variables, Pregabalin

INTRODUCTION

An ideal premedication drug should relieve anxiety, produce amnesia and sedation, decrease secretions, prevent nausea and vomiting, and suppress hemodynamic response to laryngoscopy and intubation.[1] Traditionally, benzodiazepines such as midazolam and diazepam have been used. Gabapentinoids which include gabapentin and pregabalin are new class of drugs which binds to α2-δ protein subunit of voltage-gated calcium channels and inhibits the release of excitatory neurotransmitters in the central and peripheral nervous system.[2]

The objective of our study was to compare the effect of two doses of pregabalin and diazepam as a premedication agent, on the attenuation of cardiovascular response

Access this article online

www.ijss-sn.com

Month of Submission : 06-2016
Month of Peer Review : 07-2016
Month of Acceptance : 08-2016
Month of Publishing : 08-2016

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to laryngoscopy/intubation and on the intra-operative hemodynamic parameters in patients undergoing laparoscopic cholecystectomy under general anesthesia.

MATERIALS AND METHODS

After taking approval from the Institutional Ethics Committee and written informed consent from all patients, 90 ASA I/II patients aged 20-60 years, scheduled for laparoscopic cholecystectomy under general anesthesia, were randomly divided into three groups and were premedicated as per group allotted:

- Group I: Tablet diazepam 10 mg HS and 5 mg 1 h before surgery
- Group II: Capsule pregabalin 75 mg HS and 150 mg 1 h before surgery
- Group III: Capsule pregabalin 75 mg HS and 300 mg 1 h before surgery.

Randomization was done using random number table generated from computer software. Random drug/placebo assignment in the three groups was placed in serially numbered, opaque, sealed, identical envelopes by one of the senior anesthesiologists who was not involved with the study. For external uniformity of drugs, diazepam tablets were put inside empty capsules. The anesthesiologist administering drug/conducting anesthesia was blinded to the drug administered. Patients with impaired hepatic and renal function, cardiovascular disorders, on calcium channel blockers, antidepressants and oral hypoglycemic agents, drug allergy, and pregnant were excluded from the study.

General anesthesia was induced with fentanyl citrate (1 μg/kg), thiopentone sodium (till the abolition of eyelash reflex), and rocuronium bromide (1 mg/kg). Laryngoscopy and intubation were done after 90 s, and hemodynamic parameters were recorded. No surgical intervention was allowed till 15 min after intubation. N_2O (66%), O_2 (33%), sevoflurane (1%), and injection rocuronium (0.2 mg/kg) were used for the maintenance of anesthesia. An increase in pulse rate and blood pressure (BP) (>20%), lacrimation, and sweating in the presence of normal end-tidal carbon dioxide were treated with an additional dose of fentanyl (0.5 μg/kg). Response was checked after 10 min; nonresponders were managed by an incremental increase of sevoflurane till hemodynamic normalization. Patients were reversed and trachea was extubated at the end of the surgery.

Pre- and post-operative sedation was assessed in all the three groups using 5-point scale (Table 1). Heart rate (HR) and systolic BP (SBP), diastolic BP (DBP), and mean arterial pressure (MAP) were recorded before premedication, at induction, immediately (0 min) and 1, 3, 5, 10, and 15 min after laryngoscopy, at skin incision, start of pneumoperitoneum, and every 15 min thereafter till the completion of the surgery. Electrocardiogram, SpO_2, and $EtCO_2$ were also monitored continuously throughout the procedure.

Table 1: Five-point sedation scale

Score 1 (Barely arousable)	Asleep, needs shaking or shouting to arise
Score 2 (Asleep)	Eyes closed, arousable with soft voice or light touch
Score 3 (Sleepy)	Eyes opened, less active, and responsive
Score 4	Awake
Score 5	Agitated

Assuming a 5% dropout rate, the final sample size was set at 90 patients which would permit a Type I error of α to be 5%, with a Type II error of β to be 50%, and power of 80%. The results obtained were presented in a tabulated form, and statistical analysis was performed using the Statistical Package for Social Sciences software, Windows, version 14.0. Data were analyzed using Mann–Whitney, Chi-square, ANOVA, Kruskal–Wallis, and *T*-tests as appropriate. $P < 0.05$ was considered statistically significant and <0.001 as highly statistically significant. The failure rate of the drug was defined as >30% increase in hemodynamic parameters from the baseline values.

RESULTS

Demographic data, duration of laryngoscopy, and duration of surgery were comparable in all the three groups (Table 2). Although female patients dominated in all the three groups, sex distribution was comparable.

Mean HR Comparison (*T*-test)

Group I - as shown in Table 3, there was a mild increase in HR from a basal value of 87.67 ± 14.82 beats per minute (bpm) to 91.83 ± 15.07 bpm after premedication but before the induction of anesthesia. This was increased to a highly significant value of 114.07 ± 17.52 bpm at 0 min of intubation. After that, it came down to 113.47 ± 17.29 bpm at 1 min, 112.73 ± 17.46 bpm at 3 min, 107.30 ± 15.41 bpm at 5 min, 103.27 ± 14.39 bpm at 10 min, and 97.17 ± 13.40 bpm at 15 min post-intubation, which was still highly significant as compared to the baseline values.

Group II - there was a mild increase in HR from baseline value of 86.40 ± 12.71 bpm to 91.93 ± 18.46 bpm on OT table before the induction of anesthesia. Laryngoscopy resulted in an abrupt increase to 100.73 ± 18.65 bpm at 0 min. After that, it started falling, but remained highly

significant till 3 min of laryngoscopy and significant at 5 min (94.33 ± 15.46 bpm) of laryngoscopy. It came back to almost a basal value of 90.83 ± 15.86 bpm at 10 min and even lower to 85.97 ± 10.18 bpm at 15 min post-intubation.

Group III - on OT table, mean HR increased mildly from baseline value of 86.76 ± 13.74 bpm to 90.18 ± 15.55 bpm after premedication but before the induction of anesthesia. It further increased abruptly at 0 min of laryngoscopy to 103.84 ± 18.20 bpm. The values remain highly significant only up to 3 min (101.34 ± 17.70 bpm) of laryngoscopy. After that, it started falling and became statistically insignificant at 5 min. The values almost touched to baseline at 15 min post-intubation (89.03 ± 13.75 bpm).

This shows that a rise in HR following laryngoscopy and intubation was for a shorter duration in pregabalin groups (insignificant at 10 min in Group II and at 5 min in Group III) as compared to Group I, in which the rise was still highly significant at 15 min post-intubation.

As shown in Table 3, the basal HR values were comparable between the three groups ($P \geq 0.05$). The difference in rise in HR following laryngoscopy and intubation at all time intervals (0-15 min) was highly significant between control and pregabalin groups. This difference was insignificant between Groups II and III.

MAP Comparison (*T*-test)

Group I - as shown in Table 4, there was statistically highly significant rise in MAP at 0, 1, 3, and 5 min after intubation which though started falling, reached to baseline only after 15 min (90.60 ± 9.02 mm of Hg) post-intubation.

Group II - there was a statistically insignificant and transient rise in MAP at 0 min after intubation which came below baseline at 1 min (89.23 ± 9.34 mm of Hg). After that, there was a gradual but highly significant fall in MAP till 15 min post-intubation but did not require any treatment.

Table 2: Patient characteristics

Characteristics	Group I	Group II	Group III	*P* value
Age (years)	34.97±11.95	35.50±9.46	36.97±8.22	0.73
Weight (kg)	53.47±12.32	53.83±9.79	58.33±10.91	0.17
Sex (F/M)	29/1	27/3	25/5	0.23
Duration of laryngoscopy (s)	10.10±1.73	10.40±1.59	10.30±1.68	0.46
Duration of surgery (min)	67.33±30.33	68.33±29.49	71.67±27.92	0.91

Table 3: Changes in heart rate at different time intervals following laryngoscopy and intubation

Time interval	Group I	Group II	Group III	*P* value			
				I/II	I/III	II/III	I/II/III
Before pre-medicine	87.67±14.82	86.40±12.71	86.76±13.74	0.724	0.696	0.954	0.906
Before intravenous-induced	91.83±15.07	91.93±18.46	90.18±15.55	0.982	0.162	0.210	0.343
0 min	114.07±17.52 (*P*=0.000)	100.73±18.65 (*P*=0.000)	103.84±18.20 (*P*=0.000)	0.006	0.000	0.350	0.001
1 min	113.47±17.29 (*P*=0000)	99.00±18.77 (*P*=0001)	103.33±18.22 (*P*=0.000)	0.003	0.000	0.735	0.000
3 min	112.73±17.46 (*P*=0000)	97.73±15.41 (*P*=0.002)	101.34±17.70 (*P*=0.005)	0.001	0.000	0.285	0.000
5 min	107.30±15.41 (*P*=0000)	94.33±15.46 (*P*=0.017)	97.36±16.83 (*P*=0.108)	0.002	0.000	0.329	0.000
10 min	103.27±14.39 (*P*=0000)	90.83±15.86 (*P*=0.182)	93.89±16.43 (*P*=0.613)	0.002	0.000	0.417	0.000
15 min	97.17±13.40 (*P*=0004)	85.97±10.18 (*P*=0.864)	89.03±13.75 (*P*=0.340)	0.001	0.000	0.527	0.000

P values in brackets show changes as compared to baseline (intragroup comparison)

Table 4: Changes in mean blood pressure at different time intervals following laryngoscopy and intubation

Time interval	Group I	Group II	Group III	*P* value			
				I/II	I/III	II/III	I/II/III
Before pre-medicine	90.80±11.02	90.93±8.09	90.27±8.06	0.958	0.835	0.758	0.958
Before intravenous-induced	93.73±11.13 (*P*=0.080)	91.07±9.38 (*P*=0.926)	91.83±8.01 (*P*=0.247)	0.320	0.451	0.735	0.544
0 min	110.80±12.47 (*P*=0.000)	93.93±10.13 (*P*=0.086)	95.40±10.13 (*P*=0.920)	0.000	0.000	0.577	0.000
1 min	106.13±11.59 (*P*=0.000)	89.23±9.34 (*P*=0.323)	92.07±10.31 (*P*=0.373)	0.000	0.000	0.270	0.000
3 min	99.70±11.50 (*P*=0.001)	88.17±10.93 (*P*=0.124)	89.40±9.27 (*P*=0.699)	0.000	0.000	0.639	0.000
5 min	96.03±9.74 (*P*=0.036)	84.60±10.47 (*P*=0.001)	85.50±7.87 (*P*=0.007)	0.000	0.000	0.708	0.000
10 min	91.03±8.24 (*P*=0.925)	82.77±11.20 (*P*=0.000)	83.70±8.33 (*P*=0.001)	0.002	0.001	0.716	0.002
15 min	90.60±9.02 (*P*=0.937)	80.37±9.04 (*P*=0.000)	83.17±10.58 (*P*=0.004)	0.000	0.005	0.275	0.000

P values in brackets show changes as compared to baseline (intragroup comparison)

Group III - there was statistically non-significant and transient rise in MAP at 0 min (95.40 ± 10.13 mm of Hg) and 1 min (92.07 ± 10.31 mm of Hg) after intubation. After that, there was a gradual fall in MAP which was highly significant at 3, 5, 10, and 15 min of intubation. This fall did not require any treatment clinically and came back to normal after surgical stimulus.

The above findings show that a rise in MAP following laryngoscopy and intubation was highly significant at 0-5 min interval in Group I as compared to the baseline values. Whereas pregabalin groups (II and III) showed only an insignificant rise in MAP at 0 min of intubation.

As shown in Table 4, there was a highly significant difference in Group II and Group III as compared to Group I at all time intervals (0-15 min of intubation). On the other hand, there was no statistical difference in Group II compared to Group III. The fall in MAP afterward (3-15 min) was also highly significant statistically in Group II and Group III. Although this fall was statistically significant, it was clinically insignificant and did not require any active intervention.

This shows that both pregabalin 150 mg and 300 mg were equally effective and able to attenuate MAP completely as compared to control group.

Intra-operative Hemodynamic Stability Comparison (Paired *t*-test)

Group I - As shown in Table 5, there was a definite rise in all the hemodynamic parameters; average HR (diff = +13.89), SBP (diff = +14.04), DBP (diff = +16.05), and MAP (diff = +14.93) from the baseline values during intra-operative period. In addition, all these raised parameters were both statistically as well as clinically highly significant.

Group II - there was a fall in average HR (diff = −1.40) and SBP (diff = −4.98) during intra-operative period as compared to basal values. This fall was statistically significant in case of SBP and insignificant in case of HR. In addition, there was a mild rise in average DBP (diff = +2.01) and MAP (diff = +0.34) which was statistically as well as clinically non-significant.

Group III - intraoperatively, there was a slight decrease in average SBP (diff = −0.36) as compared to baseline which is statistically insignificant. At the same time, there was a rise in average DBP (diff = +4.33), MAP (diff = +3.88), and HR (diff = +2.30) from baseline parameters. Variation in DBP and MAP was statistically significant, and in HR, it was insignificant. However, changes in all the parameters were clinically insignificant.

This shows that intra-operative hemodynamic parameters were more stable in patients who received pregabalin premedication as compared to those who received diazepam.

The above findings show that a rise in MAP following laryngoscopy and intubation was highly significant at 0-5 min interval in control group as compared to the baseline values. Whereas pregabalin groups (II and III) showed only an insignificant rise in MAP at 0 min of intubation.

Only 1 patient in Group II and 2 patients in Group III suffered dizziness, which was statistically insignificant.

DISCUSSION

Pregabalin is a new synthetic molecule and a structural derivative of the inhibitory neurotransmitter gamma-amino butyric acid. It is a α2-δ ligand that has analgesic, anticonvulsant, anxiolytic, and sleep-modulating activities. Pregabalin binds potently to the α2-δ subunit of calcium channels, resulting in a reduction in the release of several neurotransmitters, including glutamate, noradrenalin, serotonin, dopamine, and substance P.[3]

The present study was undertaken to evaluate the clinical efficacy of two different doses of pregabalin 150 mg and 300 mg as a premedicant.

Table 5: Intraoperative hemodynamic stability in all the three groups

Group	SBP before pre-medicine	SBP average intra-operative	DBP before pre-medicine	DBP average intra-operative	MBP before pre-medicine	MBP average intra-operative	HR before pre-medicine	HR average intra-operative
Group I	120.17±13.62	134.21±14.15	75.43±10.11	91.49±8.73	90.80±11.02	105.73±9.11	87.67±14.82	101.56±13.88
Difference	+14.04		+16.05		+14.93		+13.89	
P value	0.001		0.000		0.000		0.002	
Group II	119.40±9.03	114.42±9.38	77.70±10.18	79.71±8.20	90.93±8.09	91.28±8.10	86.40±12.71	84.99±10.47
Difference	−4.98		+2.01		+0.34		−1.40	
P value	0.013		0.396		0.856		0.611	
Group III	117.47±10.92	117.10±9.17	78.33±8.88	82.67±8.00	90.27±8.60	94.14±8.15	86.20±14.05	88.50±9.48
Difference	−0.36		+4.33		+3.88		+2.30	
P value	0.877		0.025		0.047		0.392	

MBP: Mean blood pressure, HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

There were no significant differences between the three groups with respect to mean age, weight, and sex of patients. The duration of laryngoscopy and duration of surgery were comparable and statistically insignificant among all the three groups.

The rise in HR following laryngoscopy and intubation was highly significant in all the three groups at 0 min of intubation. However, this rise was of shorter duration in pregabalin groups as compared to control group, in which the rise in HR was still highly significant at 15 min of intubation. In addition, intergroup comparison shows that although rise in HR was not completely attenuated by pregabalin, it had a blunting effect on HR at all time intervals (0-15 min) after laryngoscopy and intubation as compared to control group.

As far as changes in BP are concerned, the changes in SBP followed the same pattern as the changes in diastolic BP. Hence, the changes in MAP are taken as the reflection of the effect of premedication on the attenuation of pressor response to laryngoscopy and intubation. There was a highly significant rise in MAP in diazepam group at 0 min of intubation, and this rise remains statistically highly significant till 5 min. After that, it became insignificant and touched baseline only at 15 min. Whereas in pregabalin groups, a very slight rise in MAP was observed at 0 min of intubation. This rise was statistically insignificant and transient. MAP values in both these groups touched the baseline at 1 min post-intubation and followed a decreasing trend after that till 15 min in the absence of surgical stimulus. This fall was statistically significant but clinically acceptable. Intergroup comparison shows that both the doses of pregabalin were equally effective and able to attenuate pressor response completely as compared to diazepam, in which rise was highly significant from 0 to 5 min.

Our findings are in concordance with Memis *et al.* and Kong and Irwin, who studied the effect of gabapentin on the attenuation of pressor response to laryngoscopy and intubation.[4,5] A dose response study was conducted by Rastogi *et al.*[6] to evaluate the clinically effective dose of oral pregabalin for the attenuation of pressor response to intubation by administering pregabalin 75 mg and 150 mg 1 h prior to induction. They reported that the HR increased significantly immediately after laryngoscopy and intubation in all the groups, but it was least with 150 mg of pregabalin. This study also showed result similar to ours.

Memis *et al.*,[4] used gabapentin for the attenuation of cardiovascular response to laryngoscopy and intubation because of its synergistic action and analgesic properties, same as that of morphine. They found that oral administration of 800 mg gabapentin is effective in the attenuation of arterial BP and HR in 1, 3, and 5 min after laryngoscopy and endotracheal intubation. Proposed mechanism of pregabalin remains unknown. However, it is mainly due to the inhibition of calcium efflux from muscle cells with a consequent inhibition of smooth muscle relaxation, antinociceptive property, and a decrease in neuronal hyperexitability, as was hypothesized for gabapentin which might explain the effectiveness of pregabalin in the attenuation of hemodynamic response to laryngoscopy and intubation.[4,5]

A similar observation was also noted by Eren *et al.*[7] who studied the effect of pregabalin 150 mg on cardiovascular response to tracheal intubation in patients undergoing lumbar discal hernia repair. HR was significantly lower in the pregabalin group during and after intubation.

As shown in Table 5, the change in intra-operative HR and SPB, DBP, and mean BP were all in an increasing trend as compared to baseline in Group I whereas Group II/III showed either a statistically insignificant rise or a decrease in all the four parameters.

No other worker has reported the effect of pregabalin on intra-operative hemodynamic parameters. Our study shows that hemodynamic fluctuations were less in pregabalin group as compared to control group (diazepam) during the intraoperative period.

Side effects in the form of dizziness, lightheadedness, confusion, and ataxia are described with pregabalin in literature. However, in our study, only 1 patient in Group II and 2 patients in Group III suffered from dizziness which was statistically insignificant (Chi-square test).

CONCLUSION

In patients undergoing laparoscopic cholecystectomy under general anesthesia, oral pregabalin is more effective in blunting the cardiovascular response to laryngoscopy as compared to diazepam, when administered as premedication. Both pregabalin 150 mg and 300mg were equally effective in diminishing the cardiovascular response to laryngoscopy and reducing the intra-operative hemodynamic perturbations.

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How to cite this article: Saxena A, Gupta P, Chaudhary L. Effect of Pregabalin Premedication on the Laryngoscopic Response and Intra-operative Hemodynamic Variables in Laparoscopic Cholecystectomy: A Randomized Comparison of Two Doses. Int J Sci Stud 2016;4(5):75-80.

Source of Support: Nil, **Conflict of Interest:** None declared.