Comparison of Effect of Oral Midazolam and Pregabalin as Premedicants on Hemodynamic Response during General Anaesthesia in Elective Surgeries

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ABSTRACT

Background and Introduction: During GA, the hemodynamic response to laryngoscopy, endotracheal intubation, and surgical stimulation continues to be a major peri-operative problem. This sympathoadrenal activation can be harmful, particularly in patients with cardiovascular comorbidities, since it causes increased heart rate, hypertension, and an increase in mean arterial pressure. A key factor in reducing this stress reaction is optimal premedication. Pregabalin, a voltage-gated calcium channel modulator with neuromodulatory and sympatholytic effects, has emerged as a possible substitute for the traditional premedicant, midazolam, a short-acting benzodiazepine. The purpose of this study was to examine the effectiveness of oral pregabalin and midazolam as premedicants in reducing the hemodynamic response during general anesthesia during elective procedures.
Methods: This study included 54 patients undergoing planned surgery under general anesthesia, divided equally in number into Group M (oral midazolam 7.5 mg, n = 27) and Group P (oral pregabalin 150 mg, n = 27), administered 60 minutes prior to induction. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and oxygen saturation (SpO2) were recorded pre-operatively, during induction, at 1, 3, and 5 minutespost-intubation, at 30-minute, 1-hour, and 1.5-hour intraoperative intervals, at 1, 2, and 3 minutes during extubation, and in the PACU.

Results: Age ($p = 0.145$) was similar across the two groups, but weight ($p = 0.005$) and gender distribution ($p = 0.021$) were significantly different. Up to 30 minutes into the procedure, HR was similar between the groups; however, it was significantly lower in Group P at 1 hour (81.16 ± 9.89 vs 90.00 ± 11.30 bpm; $p = 0.009$) and 1.5 hours (80.15 ± 8.89 vs 89.33 ± 6.35 bpm; $p < 0.001$), during extubation at 2 minutes (92.70 ± 7.52 bpm; $p = 0.003$) and in the PACU ($p = 0.017$). From one minute after intubation until every intraoperative, extubation, and PACU timepoint, Group P had significantly reduced SBP, DBP, and MAP ($p < 0.05$ to $p < 0.001$). SpO2 remained clinically safe in both groups throughout, with no episodes of hypoxia or respiratory depression.

Conclusion: When it comes to reducing the hemodynamic response during general anesthesia in elective surgeries, oral pregabalin 150 mg is better than oral midazolam 7.5 mg. This results in much better control over BP and heart rate during the intra-operative period and during recovery, all while maintaining good oxygen saturation levels.

Keywords: Pregabalin, Midazolam, Premedication, Hemodynamic response, General anesthesia.

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INTRODUCTION

Laryngoscopy and endotracheal intubation are potent noxious stimuli producing sympathetic activation with tachycardia and hypertension.[1] These responses may precipitate myocardial ischaemia or cerebrovascular complications in susceptible patients. Several pharmacological agents have been investigated to attenuate this response, and premedication remains an important strategy.[14] Midazolam is widely used because of its anxiolytic, sedative and amnestic properties, although its haemodynamic effects are inconsistent.[2]

Endotracheal intubation and laryngoscopic manipulation, two crucial steps in the administration of general anaesthesia, are strong noxious stimuli will lead to severe hemodynamic disturbances, including a marked increase in heart rate, systemic blood pressure, and myocardial oxygen demand.

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Pregabalin binds to the α2δ subunit of voltage-gated calcium channels and reduces excitatory neurotransmitter release, thereby providing anxiolytic, analgesic and sympatholytic effects.[3] Clinical studies have demonstrated improved haemodynamic stability with pregabalin during laryngoscopy and surgery.[3,4,5,6] Therefore, this study compared oral pregabalin 150 mg with oral midazolam 7.5 mg in patients undergoing elective surgery under general anaesthesia.

AIM AND OBJECTIVES

Aim:
To compare the effect of oral Midazolam and Pregabalin as premedicants on hemodynamic response during General Anaesthesia in elective surgeries.

Objectives:

1. To assess the effectiveness of oral Pregabalin and Midazolam in attenuating hemodynamic response during surgery under general anaesthesia.
2. To compare the changes in heart rate, blood pressure and saturation in both the groups perioperatively.

MATERIALS AND METHODS

This prospective, randomized comparative study was conducted in the Department of Anaesthesiology after approval from the Institutional Ethics Committee and written informed consent from all participants. Adult patients aged 18–60 years belonging to ASA physical status I and II undergoing elective surgery under general anaesthesia were enrolled.

A total of 54 patients were randomly allocated into two equal groups (n=27 each). Group M received oral midazolam 7.5 mg, whereas Group P received oral pregabalin 150 mg, administered 60 minutes before induction of anaesthesia.

Patients with significant cardiovascular, hepatic, renal or neurological disease, pregnancy, known hypersensitivity to study drugs, anticipated difficult airway, emergency surgery, or treatment with drugs influencing haemodynamic responses were excluded.

Standard fasting guidelines were followed. In the operating room, electrocardiography, non-invasive blood pressure, pulse oximetry and other standard ASA monitors were applied. Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and oxygen saturation (SpO_2) were recorded before induction. General anaesthesia was induced and maintained using a standardized institutional protocol for all patients to minimize bias.

Haemodynamic parameters were recorded before induction, after induction, at 1, 3 and 5 minutes after endotracheal intubation, at 30 minutes, 1 hour and 1.5 hours intraoperatively, during extubation (1, 2 and 3 minutes), and in the post-anaesthesia care unit (PACU). The primary outcome was attenuation of the haemodynamic response to laryngoscopy and intubation. Secondary outcomes included perioperative blood pressure, heart rate, oxygen saturation and postoperative pain scores. Data was analysed using appropriate statistical software. Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. Student's independent t-test and Chi-square test were used where appropriate. A p value <0.05 was considered statistically significant.

SAMPLE SIZE CALCULATION

The sample size was calculated based on previous studies comparing the effects of oral premedication on hemodynamic parameters during laryngoscopy and intubation. Considering a power of 80% and a significance level of 5%, with an expected difference in mean arterial pressure of 10 mmHg between the two groups and a standard deviation of 12 mmHg, the required sample size was calculated to be 30 patients in each group. Accounting for potential dropouts and protocol violations, a total of 66 patients were planned to be enrolled, with 33 patients allocated to each group.

The Sample size formula by Difference between two means. Sample size was estimated by using the difference in Mean MAP between Group M and Group P from the study by Sahar M et al(1) as 64.7 ± 8.7 mmhg and 58.1 ± 6.2 mmhg. Using these values at 95% Confidence limit and 80% power sample size of 27 was obtained in each group by using the below mentioned formula and Med calc sample size software. With 10% nonresponse sample size of 27 + 2.7 , 30 cases will be included in each group.

FORMULA

Sample size (N) = $2SD^2(Z_{\alpha/2} + Z_{\beta})^2 / d^2$
SD – Standard deviation = From previous studies or pilot study

Za/2 = Z0.05/2 = Z0.025 = 1.96 (From Z table) at type 1error of 5% Zb = Z0.20 = 1.28 (From Z table) at 90% power d = effect size = difference between mean values

RESULTS

A total of 54 patients completed the study, with 27 patients in each group. No patient was excluded after randomization, and all participants were included in the final analysis.

The mean age of the two groups was comparable (p=0.145). Although body weight and gender distribution differed significantly between the groups, both groups were otherwise similar with respect to baseline demographic characteristics.

Baseline heart rate was comparable between the groups. No significant difference was observed during induction or within the first 30 minutes after intubation. However, from 1 hour intraoperatively onwards, the pregabalin group demonstrated significantly lower heart rate than the midazolam group, and this difference persisted during extubation and in the post-anaesthesia care unit (PACU), indicating sustained sympatholytic activity.

Table 1: Heart Rate at Different Time Points

Time Point (Mean ± SD)	Group M	Group P	p-value
Pre-op	81.85 ± 9.03	82.67 ± 8.31	0.731
During Induction	81.93 ± 10.83	83.52 ± 8.97	0.559
1 min (During Surgery)	86.33 ± 12.37	84.15 ± 7.26	0.432
3 mins (During Surgery)	85.63 ± 9.25	83.44 ± 8.01	0.358
5 mins (During Surgery)	88.07 ± 7.14	84.04 ± 8.68	0.068
1/2 (During Surgery)	88.96 ± 9.38	85.85 ± 8.58	0.209
1 (During Surgery)	90.00 ± 11.30	81.16 ± 9.89	**0.009***
1.5 (During Surgery)	89.33 ± 6.35	80.15 ± 8.89	**<0.001***
1 min (During Extubation)	94.96 ± 11.49	90.07 ± 7.08	0.065
2 mins (During Extubation)	101.04 ± 11.52	92.70 ± 7.28	**0.003***
3 mins (During Extubation)	100.15 ± 12.32	93.19 ± 7.87	**0.017***
In PACU	84.70 ± 7.97	80.00 ± 7.21	**0.027***

*statistically significant (p<0.05)

Systolic blood pressure increased after laryngoscopy and tracheal intubation in both groups; however, the increase was significantly attenuated in patients receiving pregabalin. From one minute after intubation until recovery, systolic blood pressure remained significantly lower in the pregabalin group at most observation points.

Table 2: Systolic Blood Pressure at Different Time Points

Time Point (Mean ± SD)	Group M	Group P	p-value
Pre-op	125.04 ± 14.50	116.96 ± 11.61	**0.028***
During Induction	118.67 ± 17.98	110.89 ± 12.75	**0.072***
1 min (During Surgery)	124.15 ± 20.51	106.37 ± 15.17	**0.001***
3 mins (During Surgery)	129.41 ± 18.02	106.81 ± 17.30	**<0.001***
5 mins (During Surgery)	137.48 ± 20.36	113.04 ± 17.56	**<0.001***
1/2 hr (During Surgery)	135.11 ± 18.06	115.78 ± 15.47	**<0.001***
1 hr (During Surgery)	132.69 ± 12.47	114.53 ± 11.58	**<0.001***
1.5 hr (During Surgery)	130.81 ± 6.66	120.37 ± 11.22	**<0.001***
1 min (During Extubation)	139.26 ± 17.85	121.41 ± 11.97	**<0.001***
2 mins (During Extubation)	140.22 ± 11.88	128.74 ± 16.05	**0.004***
3 mins (During Extubation)	139.26 ± 21.34	125.04 ± 14.95	**0.006***
In PACU	119.78 ± 13.96	108.96 ± 8.40	**0.001***

*statistically significant (p<0.05)

A similar trend was observed for diastolic blood pressure. Pregabalin produced significantly lower diastolic blood pressure throughout the intraoperative period, during extubation and in PACU, demonstrating superior attenuation of the sympathetic response compared with midazolam.

Table 3: Diastolic Blood Pressure at Different Time Points

Time Point (Mean ± SD)	Group M	Group P	p-value
Pre-op	77.93 ± 8.81	71.67 ± 6.56	**0.005***

Time Point (Mean ± SD)	Group M	Group P	p-value
During Induction	73.19 ± 11.36	67.63 ± 8.41	**0.046***
1 min (During Surgery)	75.11 ± 12.09	70.59 ± 10.00	**0.141***
3 mins (During Surgery)	80.59 ± 13.71	68.00 ± 12.06	**0.001***
5 mins (During Surgery)	84.96 ± 14.44	72.44 ± 11.60	**0.001***
1/2 hr (During Surgery)	83.33 ± 11.74	77.19 ± 15.00	0.100
1 hr (During Surgery)	83.54 ± 8.79	71.68 ± 7.52	**<0.001***
1.5 hr (During Surgery)	84.59 ± 7.52	78.74 ± 7.57	**0.006***
1 min (During Extubation)	88.44 ± 10.54	79.11 ± 7.32	**<0.001***
2 mins (During Extubation)	87.78 ± 9.87	80.85 ± 8.62	**0.008***
3 mins (During Extubation)	86.15 ± 13.92	78.74 ± 7.49	**0.018***
In PACU	73.26 ± 9.37	67.85 ± 8.43	**0.030***

*statistically significant (p<0.05)

Mean arterial pressure was significantly lower in the pregabalin group from one minute after intubation onward. The difference remained significant throughout surgery, extubation and recovery, reflecting improved perioperative haemodynamic stability.

Table 4: Mean Arterial Pressure at Different Time Points

Time Point (Mean ± SD)	Group M	Group P	p-value
Pre-op	93.56 ± 10.56	86.96 ± 8.18	**0.013***
During Induction	88.41 ± 12.98	83.37 ± 10.55	0.124
1 min (During Surgery)	92.63 ± 15.72	82.70 ± 11.43	**0.011***
3 mins (During Surgery)	97.63 ± 15.29	80.63 ± 13.65	**<0.001***
5 mins (During Surgery)	102.89 ± 16.34	87.00 ± 13.55	**<0.001***
1/2 hr (During Surgery)	101.15 ± 13.24	90.30 ± 14.77	**0.006***
1 hr (During Surgery)	100.46 ± 9.81	85.63 ± 8.87	**<0.001***
1.5 hr (During Surgery)	100.33 ± 6.83	92.56 ± 7.97	**<0.001***
1 min (During Extubation)	105.33 ± 11.95	93.78 ± 8.70	**<0.001***
2 mins (During Extubation)	106.11 ± 10.69	97.11 ± 11.11	**0.004***
3 mins (During Extubation)	104.33 ± 15.92	94.30 ± 9.60	**0.007***
In PACU	89.11 ± 10.90	81.48 ± 7.54	**0.004***

*statistically significant (p<0.05)

Peripheral oxygen saturation remained within clinically acceptable limits in both groups throughout the study. No episode of oxygen desaturation or respiratory depression was observed in either group, indicating comparable respiratory safety.

Table 5: Oxygen Saturation at Different Time Points

Time Point (Mean ± SD)	Group M	Group P	p-value
Pre-op	97.59 ± 1.12	98.41 ± 0.84	**0.004***
During Induction	99.78 ± 0.70	99.63 ± 0.69	0.436
1 min (During Surgery)	99.81 ± 0.96	99.63 ± 0.79	0.443
3 mins (During Surgery)	99.96 ± 0.19	99.81 ± 0.40	0.086
5 mins (During Surgery)	100.00 ± 0.00	99.74 ± 0.59	**0.028***

Time Point (Mean ± SD)	Group M	Group P	p-value
1/2 hr (During Surgery)	100.00 ± 0.00	99.74 ± 0.59	**0.028***
1 hr (During Surgery)	100.00 ± 0.00	99.79 ± 0.54	**0.050***
1.5 hr (During Surgery)	100.00 ± 0.00	99.59 ± 0.50	**<0.001***
1 min (During Extubation)	98.70 ± 0.91	99.19 ± 1.04	0.076
2 mins (During Extubation)	98.63 ± 1.04	99.07 ± 0.96	0.109
3 mins (During Extubation)	97.93 ± 1.33	99.19 ± 0.83	**<0.001***
In PACU	95.85 ± 2.23	97.89 ± 1.45	**<0.001***

*statistically significant (p<0.05)

Patients receiving pregabalin had significantly lower postoperative pain scores during the early postoperative period, particularly at the end of surgery and up to four hours postoperatively. This finding suggests an additional analgesic benefit of pregabalin as a premedicants.

Table 6: Visual Analog Scale (VAS) Scores

Time Point (Mean ± SD)	Group M	Group P	p-value
VAS Score End of Surgery	4.48 ± 1.55	3.63 ± 1.28	**0.032***
VAS at 2 hrs	5.11 ± 1.31	4.26 ± 1.26	**0.018***
VAS at 4 hrs	5.67 ± 1.18	4.67 ± 1.11	**0.002***
VAS at 6 hrs	5.77 ± 1.37	5.12 ± 1.07	0.060

*statistically significant (p<0.05)

Overall, oral pregabalin 150 mg provided superior attenuation of perioperative haemodynamic responses than oral midazolam 7.5 mg, with better control of heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure while maintaining normal oxygen saturation and improving early postoperative analgesia.

DISCUSSION

The present prospective randomized comparative study demonstrated that oral pregabalin 150 mg was more effective than oral midazolam 7.5 mg in attenuating the haemodynamic response to laryngoscopy, endotracheal intubation, surgical stimulation, extubation and early postoperative recovery. Patients receiving pregabalin showed superior control of heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure without compromising oxygen saturation.[3,4,5,6]

The demographic characteristics of the two groups were generally comparable. Although differences in body weight and gender distribution were observed, the groups were similar with respect to age and ASA physical status, allowing meaningful comparison of perioperative haemodynamic variables.[7]

Laryngoscopy and tracheal intubation are well-recognized stimuli that activate the sympathoadrenal system, producing transient tachycardia and hypertension.[12] Attenuation of this response is particularly important in patients with cardiovascular or cerebrovascular disease because excessive sympathetic stimulation may precipitate myocardial ischaemia, arrhythmias or cerebrovascular complications.[7]

In the present study, pregabalin produced sustained attenuation of heart rate from the late intraoperative period through extubation and recovery. These findings are consistent with those reported by Rastogi et al., Chandra et al. and Waikar et al., who demonstrated improved perioperative haemodynamic stability following pregabalin premedication.[8]

Pregabalin also produced significantly lower systolic, diastolic and mean arterial pressures from one minute after intubation until recovery. Similar observations have been reported by Gupta et al. and Rastogi et al., supporting the role of pregabalin as an effective oral premedicant for reducing the pressor response to airway manipulation and surgical stimulation.[8]

The favourable haemodynamic profile of pregabalin can be explained by its selective binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, resulting in reduced release of excitatory neurotransmitters including glutamate, norepinephrine and substance P.[10] This mechanism decreases central sympathetic outflow while simultaneously providing anxiolytic and analgesic effects.

Both study drugs maintained normal oxygen saturation throughout the perioperative period, and no episode of respiratory depression was observed. This finding confirms that pregabalin provides superior haemodynamic control without adversely affecting respiratory safety.[9]

An additional advantage observed in the present study was improved early postoperative analgesia with pregabalin. Lower postoperative pain scores are consistent with its established antihyperalgesic and opioid-sparing properties reported in previous clinical studies.[10]

The present study has certain limitations. The sample size was relatively small and included only ASA I–II patients undergoing elective surgery. Therefore, larger multicentre studies involving high-risk cardiovascular patients are required before these findings can be generalized.

Overall, the findings support oral pregabalin 150 mg as an effective and safe premedicant that provides superior perioperative haemodynamic stability compared with oral midazolam 7.5 mg, while also improving early postoperative analgesia.[8]

CONCLUSION

In conclusion, oral pregabalin 150 mg administered 60 minutes before induction of general anaesthesia was more effective than oral midazolam 7.5 mg in attenuating the haemodynamic response to laryngoscopy, endotracheal intubation, intraoperative surgical stimulation, extubation and the immediate postoperative period. Patients receiving pregabalin demonstrated significantly lower systolic, diastolic and mean arterial blood pressures together with superior heart rate control while maintaining comparable oxygen saturation without clinically significant respiratory depression.

Pregabalin also provided improved early postoperative analgesia, reflecting its combined anxiolytic, analgesic and sympatholytic properties. These findings suggest that pregabalin offers sustained perioperative haemodynamic stability beyond that achieved with midazolam alone.

Based on the findings of the present study, oral pregabalin 150 mg may be considered a preferred premedicant for patients undergoing elective surgery under general anaesthesia, particularly when perioperative cardiovascular stability is an important clinical objective. Larger multicentre studies involving high-risk patients are recommended to further validate these findings and broaden their clinical applicability.

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