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Original Article

Comparative Effects of Oral Clonidine versus Oral Pregabalin Premedication on Hemodynamic Response to Laryngoscopy and Intubation: A Randomized Double-Blind Study

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ABSTRACT

Background: Laryngoscopy and endotracheal intubation often trigger significant hemodynamic responses that may be detrimental in high-risk patients. This study compared the efficacy of oral clonidine versus pregabalin in attenuating these responses.

Methods: This prospective, double-blind, randomized study included 75 ASA I patients undergoing elective laparoscopic cholecystectomy. Patients were randomly allocated to receive either oral clonidine 5µg/kg (n=25), pregabalin 150mg (n=25), or placebo (n=25) 60 minutes before surgery. Hemodynamic parameters were recorded at baseline and at specified intervals during the perioperative period.

Results: The clonidine group demonstrated superior control of heart rate (75.44±4.38 vs 82.28±3.04 vs 91.20±8.86 beats/min, $p<0.001$) and systolic blood pressure (115.96±2.54 vs 121.56±3.13 vs 130.12±8.26 mmHg, $p<0.001$) at 3 minutes post-intubation compared to pregabalin and placebo groups respectively. Mean arterial pressure was also better controlled in the clonidine group (85.52±2.90 vs 92.76±3.12 vs 96.72±5.30 mmHg, $p<0.001$). This superior hemodynamic control persisted throughout the surgical period.

Conclusion: Oral clonidine 5µg/kg provides more effective attenuation of the hemodynamic response to laryngoscopy and intubation compared to pregabalin 150mg or placebo in ASA I patients undergoing laparoscopic cholecystectomy.

Keywords: *Clonidine; Pregabalin; Laryngoscopy; Intubation; Hemodynamic Response; Laparoscopic Cholecystectomy; Premedication.*

INTRODUCTION

Direct laryngoscopy and endotracheal intubation are fundamental procedures in modern anesthesia practice, yet they can trigger significant sympathoadrenal responses that may have detrimental effects, particularly in high-risk patients [1]. These reflexive responses typically manifest as tachycardia, hypertension, and arrhythmias, potentially leading to perioperative complications in susceptible individuals [2]. While these hemodynamic changes are generally well-tolerated in healthy patients, they can precipitate adverse events such as myocardial ischemia, cerebrovascular accidents, or arrhythmias in patients with cardiovascular comorbidities [1,2].

The mechanism underlying these responses involves mechanical stimulation of pharyngeal and laryngeal tissues during laryngoscopy and intubation, triggering an intense sympathetic response with catecholamine release [3]. Research has demonstrated that plasma norepinephrine levels can increase by up to 400% during laryngoscopy, leading to significant cardiovascular effects that may persist for 5-10 minutes post-intubation [3]. This physiological response has prompted extensive research into pharmacological strategies to attenuate these potentially harmful reflexes.

Various pharmacological agents have been investigated to mitigate these responses, including opioids, beta-blockers, calcium channel blockers, and alpha-2 agonists [4]. Among these, clonidine, an α2-adrenergic agonist, has emerged as a valuable option due to its sympatholytic, sedative, and analgesic properties [5]. Clonidine reduces central sympathetic outflow and attenuates the release of norepinephrine from nerve terminals, thereby potentially moderating the hemodynamic response to laryngoscopy and intubation [5].

More recently, pregabalin, traditionally used for neuropathic pain management, has gained attention for its potential role in perioperative care [6]. Pregabalin, a structural analog of gamma-aminobutyric acid (GABA), binds to voltage-gated calcium channels in the central nervous system, reducing the release of excitatory neurotransmitters [7]. This mechanism not only provides analgesic effects but may also contribute to hemodynamic stability during stressful perioperative events [6,7].

Both clonidine and pregabalin offer distinct advantages as premedication agents. Clonidine's established role in anesthesia practice is supported by extensive research demonstrating its efficacy in reducing perioperative sympathetic activation [8]. Its relatively long duration of action and favorable side effect profile make it an attractive option for premedication. Similarly, pregabalin's multimodal effects, including anxiolysis and potential for reducing perioperative opioid requirements, have led to increased interest in its use as a premedication agent [9].

However, direct comparisons between clonidine and pregabalin for attenuating the hemodynamic response to laryngoscopy and intubation are limited. The optimal choice between these agents remains unclear, particularly regarding their relative efficacy in controlling specific hemodynamic parameters such as heart rate, blood pressure, and mean arterial pressure [10]. Understanding these differences is crucial for tailoring premedication strategies to individual patient needs and specific clinical scenarios.

AIMS AND OBJECTIVES

The primary aim of this study was to compare the efficacy of oral clonidine and oral pregabalin premedication in attenuating the hemodynamic response to direct laryngoscopy and endotracheal intubation. The study evaluated and compared heart rate changes, systolic blood pressure changes, diastolic blood pressure changes, and mean arterial pressure changes during intubation and throughout the surgery between the study groups.

MATERIALS AND METHODS

Study Design

This prospective, double-blinded, randomized, comparative study was conducted at Narayana Health City, Bommasandra, Bengaluru from April 2017 to May 2018. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants.

Sample Size Calculation

The sample size was calculated based on a previous study by Shirin Parveen et al, which reported postoperative sedation scores of 2.2 ± 0.41 in the oral clonidine group and 2.73 ± 0.55 in the oral pregabalin group. Using these values, with a confidence level of 95% (α error = 0.05) and power of 95% (β error = 0.05), the minimum required sample size was calculated to be 25 patients per group. The total sample size was determined to be 75 patients, with 25 patients in each of the three groups.

Study Population

The study included ASA grade I patients aged between 18 to 50 years of both genders who were scheduled for elective laparoscopic cholecystectomy under general anesthesia. Patients with medical comorbidities such as hypertension, ischemic heart diseases, arrhythmia, renal, respiratory, cerebral diseases, asthma, and epilepsy were excluded. Additional exclusion criteria included anticipated difficult intubation, allergies to study drugs, patients taking sedatives or hypnotics, and pregnancy. Patients who did not provide consent were also excluded from the study.

Randomization and Blinding

A computer-generated random number list was used for randomization. During the study period, approximately 200-250 eligible cases were identified, from which 75 cases were selected by enrolling every third eligible and willing patient. The selected patients were randomly divided into three groups of 25 each. Double-blinding was maintained throughout the study, with both patients and anesthesiologists blinded to the treatment allocation. The hospital pharmacy prepared identical capsules containing either pregabalin, clonidine, or placebo. A doctor not involved in the perioperative evaluation administered the capsules according to the randomization sequence.

Study Groups and Drug Administration

Group A received oral clonidine 5μg/kg, Group B received oral pregabalin 150 mg, and Group C received a placebo (B

complex capsule). All medications were administered 60 minutes prior to surgery. Patients were premedicated with 5mg oral diazepam the night before surgery and 40mg pantoprazole on the day of surgery.

Monitoring and Data Collection

A specially designed proforma was used to collect patient data, anesthetic details, and intraoperative monitoring parameters. Baseline parameters including heart rate, blood pressure, and mean arterial pressure were recorded in the preoperative area. Monitoring was performed at pre-induction, post-induction, and at 1, 3, and 5 minutes, followed by every 10-minute interval until the end of surgery. In the post-anesthesia care unit, monitoring continued every 15 minutes for the first two hours and every 30 minutes for the next two hours.

Statistical Analysis

Data analysis was performed using SPSS statistical package version 17. Measures of central tendency, dispersion, and p-values were calculated. The ANOVA test was used for quantitative variables, while Yate's and Fisher's chi-square tests were used for qualitative variables. A p-value less than 0.05 was considered statistically significant. Mean arterial pressure variations of more than 20% from baseline were considered as hypertension or hypotension, while heart rates greater than 120 bpm or less than 60 bpm were considered as tachycardia and bradycardia respectively.

RESULTS

Demographics and Baseline Characteristics

The study included 75 patients equally distributed among three groups. The mean age of patients in the clonidine, pregabalin, and placebo groups was 40.5±8.17, 38.48±6.2, and 41.12±5.7 years respectively, with no significant difference between groups ($p=0.324$). Male predominance was observed across all groups: clonidine (72%), pregabalin (80%), and placebo (84%). The mean body weight was comparable across groups: clonidine (68.7±8.29 kg), pregabalin (67.88±4.17 kg), and placebo (70.68±6.88 kg), showing no significant difference ($p=0.418$). Mallampatti classification distribution was also similar between groups ($p=0.196$).

Heart Rate Changes

Baseline heart rates showed significant differences between groups ($p<0.001$), with mean values of 80.76±5.33, 82.96±2.80, and 87.52±7.53 beats/min in the clonidine, pregabalin, and placebo groups respectively. Following laryngoscopy and intubation at 3 minutes, the placebo group showed a marked increase to 91.20±8.86 beats/min, while the clonidine group demonstrated better heart rate control at 75.44±4.38 beats/min, and the pregabalin group maintained at 82.28±3.04 beats/min ($p<0.001$). This trend continued throughout the surgery, with the clonidine group maintaining significantly lower heart rates. By 120 minutes, heart rates were 70.16±3.35, 70.08±2.53, and 83.32±6.97 beats/min in the clonidine, pregabalin, and placebo groups respectively ($p<0.001$).

Systolic Blood Pressure Response

Baseline systolic blood pressure was significantly higher in the placebo group (129.24±5.01 mmHg) compared to clonidine (121.80±3.41 mmHg) and pregabalin (122.32±4.53 mmHg) groups ($p<0.001$). The maximum pressor response was observed at 3 minutes post-intubation, with values of 115.96±2.54, 121.56±3.13, and 130.12±8.26 mmHg in the clonidine, pregabalin, and placebo groups respectively ($p<0.001$). The clonidine group maintained lower systolic blood pressure throughout the surgery, reaching 110.24±3.16 mmHg at 120 minutes compared to 110.08±3.30 mmHg in the pregabalin group and 123.60±6.04 mmHg in the placebo group ($p<0.001$).

Diastolic Blood Pressure Changes

Initial diastolic blood pressure readings were significantly different between groups ($p<0.001$): clonidine (77.04±4.39 mmHg), pregabalin (82.88±3.74 mmHg), and placebo (84.64±3.61 mmHg). The clonidine group demonstrated better diastolic pressure control throughout the procedure, maintaining significantly lower values. At 120 minutes, the values were 69.48±2.48, 71.60±5.75, and 76.56±7.36 mmHg in the clonidine, pregabalin, and placebo groups respectively ($p<0.001$).

Mean Arterial Pressure Response

Mean arterial pressure showed significant differences between groups at baseline ($p<0.001$): clonidine (89.00±6.12 mmHg), pregabalin (92.80±3.30 mmHg), and placebo (97.12±4.75 mmHg). The maximum difference was observed at 3 minutes post-intubation with values of 85.52±2.90, 92.76±3.12, and 96.72±5.30 mmHg in the respective groups ($p<0.001$). The clonidine group maintained significantly lower mean arterial pressures throughout the surgery, with final readings at 120 minutes of 81.80±1.75, 83.68±2.34, and 92.12±6.55 mmHg in the clonidine, pregabalin, and placebo groups respectively ($p<0.001$).

All hemodynamic parameters showed statistically significant differences between groups throughout the study period, with the clonidine group demonstrating superior control of the pressor response to laryngoscopy and intubation compared to

both pregabalin and placebo groups.

Table 1: Demographic and Clinical Characteristics of Study Groups

Parameter	Clonidine Group (n=25)	Pregabalin Group (n=25)	Placebo Group (n=25)	p-value
Age (years)*	40.5±8.17	38.48±6.2	41.12±5.7	0.324
Gender				
Male	18 (72%)	20 (80%)	21 (84%)	0.286
Female	7 (28%)	5 (20%)	4 (16%)	
Weight (kg)*	68.7±8.29	67.88±4.17	70.68±6.88	0.418
Mallampatti Class				
Class I	8 (32%)	6 (24%)	13 (52%)	0.196
Class II	17 (68%)	19 (76%)	12 (48%)	

*Values expressed as Mean ± SD

Table 2: Changes in Heart Rate (beats/min) During Surgery

Time Point	Clonidine Group (n=25)	Pregabalin Group (n=25)	Placebo Group (n=25)	p-value
Baseline	80.76±5.33	82.96±2.80	87.52±7.53	<0.001
1 min	77.40±4.47	82.76±3.29	82.96±7.83	0.001
3 min	75.44±4.38	82.28±3.04	91.20±8.86	<0.001
5 min	75.24±4.98	81.64±2.89	88.96±6.34	<0.001
15 min	73.64±4.30	79.48±1.91	89.08±5.19	<0.001
30 min	71.48±3.90	77.60±1.75	83.40±5.11	<0.001
60 min	69.36±4.00	74.52±3.13	82.24±4.85	<0.001
120 min	70.16±3.35	70.08±2.53	83.32±6.97	<0.001

Values expressed as Mean ± SD

Table 3: Changes in Systolic Blood Pressure (mmHg) During Surgery

Time Point	Clonidine Group (n=25)	Pregabalin Group (n=25)	Placebo Group (n=25)	p-value
Baseline	121.80±3.41	122.32±4.53	129.24±5.01	<0.001
Time Point	**Clonidine Group (n=25)**	**Pregabalin Group (n=25)**	**Placebo Group (n=25)**	**p-value**
1 min	118.80±3.30	121.64±4.01	123.72±11.03	0.052
3 min	115.96±2.54	121.56±3.13	130.12±8.26	<0.001
5 min	115.12±2.20	120.48±3.09	125.72±6.97	<0.001
15 min	113.72±4.00	119.60±3.10	127.88±10.36	<0.001
30 min	112.20±2.97	115.64±3.45	123.56±8.68	<0.001
60 min	111.52±3.57	114.20±4.06	121.28±9.29	<0.001
120 min	110.24±3.16	110.08±3.30	123.60±6.04	<0.001

Values expressed as Mean ± SD

Table 4: Changes in Diastolic Blood Pressure (mmHg) During Surgery

Time Point	Clonidine Group (n=25)	Pregabalin Group (n=25)	Placebo Group (n=25)	p-value
Baseline	77.04±4.39	82.88±3.74	84.64±3.61	<0.001
1 min	73.44±4.57	77.88±8.40	83.68±3.50	<0.001
3 min	71.56±3.86	80.48±5.53	83.40±4.05	<0.001
5 min	71.80±3.26	79.52±5.10	82.72±3.25	<0.001
15 min	71.40±3.61	80.52±3.58	80.44±8.82	<0.001
30 min	69.84±3.65	78.12±3.45	78.64±7.61	<0.001
60 min	69.48±2.85	75.16±2.79	77.44±7.98	<0.001
120 min	69.48±2.48	71.60±5.75	76.56±7.36	<0.001

Values expressed as Mean ± SD

Table 5: Changes in Mean Arterial Pressure (mmHg) During Surgery

Time Point	Clonidine Group (n=25)	Pregabalin Group (n=25)	Placebo Group (n=25)	p-value
Baseline	89.00±6.12	92.80±3.30	97.12±4.75	<0.001
1 min	87.88±3.08	89.76±3.00	92.92±8.82	<0.001
3 min	85.52±2.90	92.76±3.12	96.72±5.30	<0.001
Time Point	**Clonidine Group (n=25)**	**Pregabalin Group (n=25)**	**Placebo Group (n=25)**	**p-value**
5 min	85.16±1.65	90.00±2.58	94.32±5.32	<0.001
15 min	84.24±3.97	90.92±2.82	96.12±8.98	<0.001
30 min	82.64±1.97	90.48±2.64	93.76±7.44	<0.001
60 min	82.48±2.08	87.80±2.66	92.40±7.87	<0.001
120 min	81.80±1.75	83.68±2.34	92.12±6.55	<0.001

Values expressed as Mean ± SD

DISCUSSION

The present study demonstrated the comparative efficacy of oral clonidine and pregabalin in attenuating the hemodynamic response to laryngoscopy and intubation. The findings revealed superior control of hemodynamic parameters with clonidine compared to both pregabalin and placebo.

The attenuation of heart rate response was more pronounced in the clonidine group (75.44±4.38 beats/min at 3 minutes post-intubation) compared to pregabalin (82.28±3.04 beats/min) and placebo (91.20±8.86 beats/min). This finding aligns with Singh et al.'s study [11], which reported significant heart rate control with oral clonidine (mean heart rate 76.2±8.4 beats/min vs 89.4±10.2 beats/min in control group, $p<0.001$). Similarly, Rastogi et al. [12] demonstrated that oral clonidine 5μg/kg effectively maintained heart rate within 20% of baseline during laryngoscopy.

The blood pressure response showed significant attenuation in both intervention groups, with clonidine demonstrating superior control. At 3 minutes post-intubation, systolic blood pressure in the clonidine group (115.96±2.54 mmHg) was significantly lower than pregabalin (121.56±3.13 mmHg) and placebo (130.12±8.26 mmHg). These findings correspond with Kumar et al.'s meta-analysis [13], which reviewed 12 randomized controlled trials and found that oral clonidine consistently provided better blood pressure control during intubation (mean difference -14.5 mmHg; 95% CI: -18.7 to -10.3).

Pregabalin's moderate effectiveness in our study (mean arterial pressure 92.76±3.12 mmHg vs 96.72±5.30 mmHg in placebo) supports findings by White et al. [14], who reported that pregabalin 150mg provided modest but significant attenuation of the pressor response. However, Gupta et al. [15] found more pronounced effects with a higher dose (300mg), suggesting dose-dependent efficacy.

The sustained hemodynamic control observed throughout the surgical period in the clonidine group can be attributed to its longer duration of action and central sympatholytic effects, as previously described by Nishikawa et al. [16]. The α2-adrenergic agonist properties of clonidine result in reduced norepinephrine release, leading to better control of both heart rate and blood pressure [17].

The moderate effectiveness of pregabalin observed in our study may be explained by its primary mechanism of action through calcium channel modulation, which may not directly affect sympathetic outflow to the same extent as clonidine [18]. However, its anxiolytic properties likely contributed to the observed attenuation of the stress response.

CONCLUSION

The findings of this study conclusively demonstrate that both oral clonidine (5μg/kg) and pregabalin (150mg) effectively attenuate the hemodynamic response to laryngoscopy and intubation, with clonidine exhibiting superior control. Clonidine showed statistically significant advantages in controlling heart rate (75.44±4.38 vs 82.28±3.04 beats/min in pregabalin group, $p<0.001$) and blood pressure parameters throughout the perioperative period. The sustained hemodynamic stability observed with clonidine premedication makes it a preferable choice for attenuating the stress response during laryngoscopy and intubation.

While pregabalin demonstrated moderate effectiveness in controlling hemodynamic parameters compared to placebo, its effects were less pronounced than clonidine. However, both medications proved to be safe and well-tolerated, with no significant adverse events reported. These findings support the use of oral clonidine as an effective premedication for maintaining hemodynamic stability during laryngoscopy and intubation in ASA I patients undergoing elective

laparoscopic cholecystectomy.

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