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A COMPARISON OF ORAL PREGABALIN AND ORAL CLONIDINE FOR THE ATTENUATION OF HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION AND THE TIME FOR RESCUE ANALGESIC IN THYROID SURGERIES

Anaesthesiology

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ABSTRACT

Background and Aims: Our study had been designed to compare the effect of oral pregabalin and clonidine on cardiovascular response from laryngoscopy and endotracheal intubation and also to find the time for rescue analgesia in patients undergoing thyroidectomies.
Materials and Methods: 78 adult patients scheduled for thyroid surgeries were divided randomly into two groups. Group C received clonidine 200 µg and Group P received pregabalin 150 mg as oral premedication. The heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were recorded serially. Time for rescue analgesia in the postoperative period was also noted.
Results: Clonidine showed significantly better attenuation of stress response to laryngoscopy and intubation than pregabalin. The mean time for rescue analgesia after thyroidectomy was higher in pregabalin group.
Conclusion: Attenuation of hemodynamic response of laryngoscopy and intubation was better with clonidine whereas pregabalin was a better analgesic.

KEYWORDS

Pregabalin, Clonidne, Laryngoscopy, Thyroidectomy

INTRODUCTION

Laryngoscopy and tracheal intubation are noxious stimuli which evoke a transient but marked sympathetic response manifesting as increase in heart rate (HR) and blood pressure (BP). In patients with cardiovascular disease, these hemodynamic changes can lead to life-threatening complications such as acute heart failure, myocardial ischemia, and cerebrovascular accidents.[1]

Conventional treatment methods include topical lignocaine sprays, deeper planes of anaesthesia, calcium channel blockers, and vasodilators such as sodium nitroprusside and nitroglycerine.[2] Although there are various methods, research is still in progress for techniques of attenuation of stress response to laryngoscopy and intubation.[3]

Clonidine is an α-2 adrenoreceptor agonist with central sympatholytic effect. Premedication with clonidine blunts the haemodynamic stress responses to direct laryngoscopy and tracheal intubation. Clonidine also stabilizes blood pressure by increasing cardiac baroreceptor reflex sensitivity.[4]

Pregabalin, a gabapentinoid compound appears to produce an inhibitory modulation of neuronal excitability particularly in neocortex, amygdala and hippocampus of CNS.[5] It possesses analgesic, anticonvulsant and anxiolytic activity by reduction of neurotransmitter glutamate, nor-adrenaline, serotonin, dopamine and substance P.[5]

Effective management of postoperative pain leads to increased patient satisfaction, earlier mobilization, reduced hospital stay and costs. Poorly managed acute pain that might occur following surgery can produce pathophysiologic processes in both the peripheral and the central nervous systems (CNS) that have detrimental acute and chronic effects.[6] Hence, pain management is important especially in the early postoperative period after thyroidectomy. Pregabalin and clonidine have been used as preemptive analgesic in the postoperative period.

The present study has been designed to evaluate and compare the effects of oral pregabalin and clonidine in attenuating the pressor response to laryngoscopy and endotracheal intubation and to determine the time for requirement of rescue analgesic in thyroid surgeries.

OBJECTIVES OF THE STUDY

1. To evaluate and compare the effect of oral pregabalin and clonidine on cardiovascular response resulting from laryngoscopy and endotracheal intubation in thyroid surgeries.
2. To determine and compare the time for requirement of rescue analgesia in patients premedicated with oral pregabalin and clonidine.

METHODOLOGY

After taking written informed consent, 78 subjects belonging to ASA I and II scheduled for thyroidectomy were included. They were divided into two groups of 39 each.

Group C (Clonidine)
Group P (Pregabalin)

a) Inclusion criteria**:** ASA physical status Classes I or II aged between 18-50 yrs undergoing thyroidectomy surgery
b) Exclusion criteria: Uncooperative and unwilling patient**,** or patients with hypersensitivity to drugs or with the history of cerebrovascular, neurologic, respiratory or cardiovascular diseases, renal and hepatic dysfunction, any predicted difficult airway or patients in whom laryngoscopy exceeded 15 seconds.

A detailed history and complete clinical examination of patients were done to rule out the exclusion criteria. ECG, whenever indicated, was taken. Preoperative HR, respiratory rate, BP values were noted. Written and informed consent was taken prior to the scheduled operation.

Following approval of institutional ethics committee, 78 patients were taken up for the study. Patients were kept nil per oral from midnight. They were premedicated with diazepam 5 mg orally and ranitidine 150 mg orally the previous night. Patient's baseline vitals i.e. systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and HR were recorded.

As the sample size is 78, 39 patients allocated to Group C received oral clonidine 200 µg 90 min prior to surgery and remaining 39 allocated to Group P received oral pregabalin 150 mg 90 min prior to surgery.

On shifting to OT, intravenous access was obtained by an 18 G IV cannula. Standard monitors like pulse oximetry, non-invasive blood pressure and electrocardiography were connected to the patient. The patient was administered IV fluid Ringer's lactate and the vitals before induction i.e. HR, SBP, DBP and MAP and oxygen saturation were recorded.

General anaesthesia technique was standardized to all patients. All patients were administered fentanyl 2 ug/kg IV. After pre-oxygenation for 3 minutes, anaesthesia was induced with propofol 2 mg/kg and IV succinyl choline 2mg/kg was given. Hemodynamic parameters were recorded after induction.

Intubation was done using laryngoscope with a Macintosh blade, with appropriate sized cuffed oral endotracheal tube. After confirmation of the tube position, cuff was inflated, tube fixed and connected to the ventilator.

Once the patient was intubated the following haemodynamic responses were recorded at 0, 1, 3 and 5 and 10 mins- HR, SBP, DBP and MAP.

Anaesthesia was maintained with 33% oxygen, 66% nitrous oxide and isoflurane 0.6% on controlled ventilation. Neuromuscular blockade was maintained with vecuronium bromide 0.1 mg/kg IV after induction and regular top-ups of 0.02 mg/kg. After surgery, reversal was achieved with IV neostigmine 0.05 mg/kg and IV glycopyrrolate 0.01 mg/kg.

Postoperatively, rescue analgesia was administered at the request of the patient. The time duration from the end of surgery to the first analgesic dose was recorded and IV paracetamol 1 g was given.

RESULTS

The study involved a total of 78 patients belonging to ASA class I and II posted for thyroidectomy under general anaesthesia. They were divided into two groups of 39 each i.e Group C (Clonidine group) and Group P (Pregabalin group).

Both groups were comparable with respect to demographic profile (age, gender, height and weight) (Table 1) and no statistically significant difference ($p > 0.05$) was observed in the duration of surgery and baseline hemodynamic parameters.

Table 1: Demographic data of both groups

	Group C	Group P	p Value
Age (yrs)	51.03 ± 8.100	47.59 ± 11.684	0.136
Sex (Female/Male)	32/7	31/8	0.083
Weight (kg)	61.05 ± 7.609	63.72 ± 8.473	0.148
Height (cm)	166.26 ± 4.833	166.69 ± 5.317	0.706

*p value < 0.05 is significant

The SBP in the two groups before and after induction was comparable. Both groups showed rise in SBP immediately after intubation, however, the rise in group C (117.15 ± 11.357) was less when compared to the group P (122.54 ± 9.101) and this was statistically significant. Thereafter, SBP consistently decreased and the difference between the two groups was statistically significant at 1 min, 3 min and 5 min after intubation ($p < 0.05$) with clonidine showing better control (Table 2).

Table 2: Comparison of mean systolic blood pressure between the two groups at different time intervals

Time (min)	Group C	Group P	p Value
Before induction	127.90 ± 12.494	125.41 ± 5.354	0.258
After induction	102.46 ± 8.991	104.77 ± 5.188	0.170
Immediately after intubation	117.15 ± 11.357	122.54 ± 9.101	0.024*
1 min after intubation	114.82 ± 9.017	119.18 ± 7.059	0.020*
3 min after intubation	104.31 ± 8.259	108.87 ± 10.339	0.035*
5 min after intubation	103.82 ± 10.036	108.92 ± 9.601	0.025*
10 min after intubation	102.46 ± 9.670	103.03 ± 6.949	0.768

Values are in mean ± SD
*p value < 0.05 is significant

DBP was better controlled in group C when compared to Group P after induction. After intubation, there was less increase in the DBP in group C (76.28 ± 9.293) than group P (80.538 ± 9.156) and this difference was statistically significant ($p < 0.05$) immediately after intubation and at 1 min and 3 min after intubation (Table 3).

Table 3: Comparison of mean diastolic blood pressure between the two groups at different time intervals

Time (min)	Group C	Group P	p Value
Before induction	75.59±10.522	73.95 ± 4.828	0.380
After induction	65.97 ± 7.143	66.051 ± 5.995	0.959
Immediately after intubation	76.28 ± 9.293	80.538 ± 9.156	0.045*
1 min after intubation	72.72 ± 68.87	77.760 ± 12.370	0.038*
3 min after intubation	68.87 ± 7.310	73.615 ± 12.493	0.045*
5 min after intubation	68.05 ± 7.960	69.385 ± 10.973	0.541
10 min after intubation	66.10 ± 6.824	68.410 ± 9.533	0.223

Values are in mean ± SD
*p value < 0.05 is significant

The MAP was comparable between the two groups before and after induction. After intubation there was a rise in MAP in both the groups but was better controlled in group C and this was statistically significant ($p < 0.05$) immediately after intubation and also at 1 and 3 min after intubation. Thereafter, the difference was not statistically significant (Table 4).

Table 4: Comparison of mean arterial pressure between the two groups at different time intervals

Time (min)	Group C	Group P	p Value
Before induction	75.59 ± 10.522	73.95 ± 4.828	0.380
After induction	65.97 ± 7.143	66.051 ± 5.995	0.959
Immediately after intubation	76.28 ± 9.293	80.538 ± 9.156	0.045*
1 min after intubation	72.72 ± 68.87	77.760 ± 12.370	0.038*
3 min after intubation	68.87 ± 7.310	73.615 ± 12.493	0.045*
5 min after intubation	68.05 ± 7.960	69.385 ± 10.973	0.541
10 min after intubation	66.10 ± 6.824	68.410 ± 9.533	0.223

Values are in mean ± SD
*p value < 0.05 is significant

At all observation periods, the HR of clonidine group was found to be lower than that of pregabalin group. The mean HR in the clonidine group was less than the group receiving pregabalin and was statistically significant ($P < 0.05$) after induction. Immediately after laryngoscopy and intubation, the HR increased in both the groups, but was less in group C (73.85 ± 6.815) as compared to group P (82.05 ± 11.316) which was highly significant (p value < 0.001). Subsequently, both groups controlled the HR which was significantly lower in clonidine group when compared to pregabalin group and at 1 min, 3 min, 5 min and 10 min after intubation (Table 5).

Table 5: Comparison of mean heart rate between the two groups at different time intervals

Time (min)	Group C	Group P	p Value
Before induction	67.46 ± 7.225	70.54 ± 6.770	0.056
After induction	61.59 ± 6.244	67.36 ± 7.054	<0.001#
Immediately after intubation	73.85 ± 6.815	82.05 ± 11.316	<0.001#
1 min after intubation	67.54 ± 7.957	81.59 ± 9.273	<0.001#
3 min after intubation	67.23 ± 7.191	81.74 ± 6.711	<0.001#
5 min after intubation	64.33 ± 6.607	79.39 ± 5.556	<0.001#
10 min after intubation	63.08 ± 6.032	77.95 ± 5.871	<0.001#

Values are in mean ± SD
#p value < 0.001 is highly significant

The mean time for rescue analgesia in minutes was higher in Group P (206.56 ± 9.349 min) than in Group C (185.13 ± 5.161 min) and this difference was statistically highly significant (p value < 0.001, Fig 1).

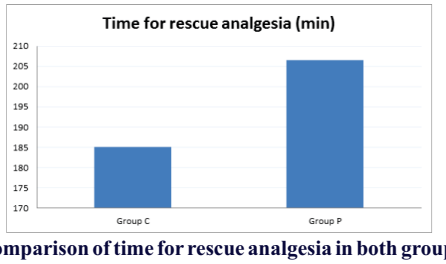

Fig 1. Comparison of time for rescue analgesia in both groups

DISCUSSION

This study was conducted to compare the effects of oral clonidine 300 µg versus oral pregabalin (150mg) premedication on attenuation of stress response to direct laryngoscopy and tracheal intubation and the time for rescue analgesic in patients undergoing thyroidectomy surgery.

Laryngoscopy and intubation are associated with cardiovascular changes such as hypertension, tachycardia, dysrhythmias and even myocardial ischemia and increased circulating catecholamines.[1,2] These changes are well tolerated in healthy individuals but can have detrimental effects on patients with cardiovascular compromise.[7] Several techniques have been employed to prevent or attenuate the hemodynamic responses following laryngoscopy and intubation, such as deepening the plane of anaesthesia and use of vasodilators such as nitroglycerin, lignocaine, beta-blockers, calcium channel blockers,

and opioids.[8] However, search for the ideal premedicant with minimal side effects is underway.

Clonidine is an α-2 adrenoreceptor agonist with central sympatholytic effect. It attenuates the stress response of laryngoscopy by activating central α2 adrenoreceptors which decreases peripheral sympathetic tone and stimulates the peripheral presynaptic α2 adrenoreceptors which leads to decreased norepinephrine release from nerve endings, and hence reduces peripheral sympathetic tone.[9]

Pregabalin is a gabapentinoid compound, an antiepileptic drug, and acts by inhibiting membrane voltage-gated calcium channels in central nervous system. It does not interact with GABA receptors. It has anticonvulsant, analgesic and anxiolytic properties. It is effective in controlling neuropathic pain. Several mechanisms may contribute to the attenuation of pressor response by pregabalin, which include the modulation of visceral pain and central sensitization. Pregabalin inhibits membrane voltage-dependent Ca2+ channels acting in a manner similar to calcium channel blockers in controlling the hemodynamic response.[10]

Our study has shown that both clonidine and pregabalin attenuated the hemodynamic response to laryngoscopy and endotracheal intubation. However, clonidine showed significantly better control of hemodynamic parameters as compared to pregabalin. The SBP, DBP, MAP and HR were less post intubation.

Our study findings correlate with those of Gupta *et al.*[8], Rathore *et al.*[11] who demonstrated that both clonidine and pregabalin reduced the hemodynamic response to laryngoscopy and intubation with clonidine showing better hemodynamic stability than pregabalin. The doses of study drugs that they have used in their studies are the same as those of the current study. However, Gupta *et al.* used only 1 µg/kg fentanyl IV as premedication in their study as compared to 2 µg/kg fentanyl IV we used in our study. Rathore *et al.* did not use any opioids as part of their premedication as we did.

Our study has shown that the time for rescue analgesic was higher with pregabalin than with clonidine. The mean time for rescue analgesic in pregabalin group was 206.56 ± 9.349 min. Bindu *et al.*[12] had studied the effect of preoperative pregabalin on postoperative pain relief in thyroidectomy patients and observed that the average time for rescue analgesic for pregabalin was 322.07 ± 69.106 min. But this prolonged time in their study could be due to the fact that they used a higher dose of pregabalin (300 mg). This is in accordance with the meta-analysis conducted by Hu *et al.*[13] on the effects of a single dose of preoperative pregabalin and gabapentin for acute postoperative pain. They have concluded that a dose–response relationship exists with respect to opioid consumption and postoperative pain for a single-dose preoperative administration of pregabalin. Likewise, the time for rescue analgesia for clonidine group in our study was 185.13 ± 5.161 min. This was in agreement with a previous study done by Singh *et al.*[14] who evaluated the effect of oral clonidine premedication 150 µg on perioperative haemodynamic response and post-operative analgesic requirement for patients undergoing laparoscopic cholecystectomy and they also observed a similar time for rescue analgesia (185 ± 34.4 min). However, the difference from our study is that we recorded the time for rescue analgesia in thyroidectomy patients.

CONCLUSION

Both clonidine and pregabalin are effective oral premedicant drugs for attenuation of the hemodynamic response of laryngoscopy and endotracheal intubation. However, clonidine showed better control of hemodynamics after intubation when compared to pregabalin. Both drugs have shown efficacy in decreasing the perioperative analgesic requirement with pregabalin faring better than clonidine.

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