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Original Article

Anaesthesia Section

Comparison of Oral Labetolol and Oral Pregabalin in Attenuating Pressor Response to Endotracheal Intubation in Patients undergoing Mastoidectomy under General Anaesthesia- A Randomised Control Study

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ABSTRACT

Introduction: Direct laryngoscopy and tracheal intubation provoke stress response side-effects in the form of hypertension, tachycardia, and dysrhythmia which are long-standing concerns for anaesthetists. Various drugs and techniques have been tried over the last few decades to avoid these side-effects but none are ideal. Oral labetalol through years of study has proven its efficacy in attenuation of these haemodynamic responses. Oral pregabalin is also effective in this regard, however, there are no studies comparing their relative efficacies. In the present study, we have compared these two drugs i.e., oral pregabalin and oral labetalol with satisfactory results.

Aim: To compare the efficacy of preoperative oral pregabalin with that of oral labetalol in controlling the haemodynamic responses to laryngoscopy and intubation in patients undergoing mastoidectomy under general anaesthesia.

Materials and Methods: This randomised control study was conducted in Era Medical College and Hospital, Lucknow, Uttar Pradesh, India, over the period of 18 months from June 2019 to December 2020. Total 90 American Society of Anesthesiologists (ASA) Grade I and II patients aged 18-50 years of either gender scheduled to undergo elective mastoidectomy surgery under general anaesthesia were enrolled in this study. Thirty patients received tablet oral pregabalin 150 mg, 30 received oral labetalol tablet 200 mg while the remaining 30 received placebo in form of a multivitamin tablet. Drugs were given one hour before propofol induction. Heart rate, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Arterial Pressure (MAP) were recorded preoperatively, 60 minutes after administration of study drug, during laryngoscopy and intubation, and at 1, 2, 5, and 10 minutes after intubation. At the end of the study, results were represented as (mean±SD) and percentage changes and compared using the student's t-test.

Results: Mean age of group I was 25.53±8.51 years, group II was 24.80±8.19 years and group III was 26.03±9.10 years. While conducting an intergroup comparison of the two study drugs oral pregabalin showed a greater control in haemodynamic parameters like SBP (at t=2 min, p-value <0.001, t=5 min, p-value 0.003), DBP {at t=Induction (p-value <0.001), 1 min (p-value=0.010), 2 min (p-value <0.001), 5 min (p-value <0.001)} and MAP {at t=Induction (p-value <0.001), 1 min (p-value=0.006), 2 min (p-value <0.004), 5 min (p-value=0.033)} than oral labetalol. Intergroup difference in heart rate was not appreciable between the two drugs except at 60 minutes and baseline after administration (p-value <0.001).

Conclusion: The study showed that though both pregabalin and labetalol were effective in controlling postintubation haemodynamic changes, attenuation of all immediate postintubation haemodynamic changes except heart rate was more effective with pregabalin as compared to labetalol. The difference in attenuation of heart rate was not significant between pregabalin and labetalol.

Keywords: β-Blockers, Direct laryngoscopy, Gabapentinoids, Haemodynamic, Stress response

INTRODUCTION

Laryngoscopy and tracheal intubation is a noxious stimulus [1] that provokes a stress response, particularly in the cardiovascular system in the form of hypertension, tachycardia [2], and dysrhythmia [1,2]. To attenuate the haemodynamic response, many pharmacological agents have been tried but to date, no agent has been found free of complications, and thus none is ideal.

Pregabalin, a gabapentinoid compound, is structurally (but not functionally) related to the inhibitory neurotransmitter Gamma-Aminobutyric Acid (GABA). It acts by decreasing the synthesis of the neurotransmitter glutamate in the central nervous system. It possesses analgesic, anticonvulsant and anxiolytic properties and is effective in preventing the neuropathic component of acute nociceptive pain of surgery [3]. It is well absorbed and tolerated after oral administration, with peak plasma concentrations occurring within 60-90 minutes. It undergoes negligible hepatic metabolism [3].

Labetalol, introduced in 1976 is an α and β receptor antagonist. It has traditionally been used in the control of both arterial Blood Pressure (BP) and Heart Rate (HR). It is lipid-soluble, undergoes considerable hepatic first-pass metabolism, and is readily absorbed after oral administration. It has a bioavailability of around 25%. The peak plasma concentrations are generally achieved within two hours [4,5].

Various studies over the years have proven the efficacy of labetalol in controlling the stress responses of intubation efficiently [6,7]. Overall, labetalol is usually well-tolerated and most adverse effects are typically mild and transient. But in patients with impaired left ventricular function, acute left ventricular failure might occur [4]. This along with the fact that labetalol is known to cause symptomatic postural hypotension [4,5], warranted the need to search for alternatives. Pregabalin has also been shown to be effective in controlling stress responses to laryngoscopy [8,9] and since pregabalin has no effect on heart, chances of cardiovascular

compromise are limited. Though many studies have been done in regard to its role in attenuation of pressor response to endotracheal intubation, none have compared it with labetalol. The present study was thus designed to determine how well does oral pregabalin fares against oral labetalol and against a control group. Primary outcomes measured were the haemodynamic parameters {Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Arterial Pressure (MAP)}. Secondary outcomes were to note any side-effects like nausea, vomiting, postural hypotension or any allergic reactions.

MATERIALS AND METHODS

This randomised control study was conducted in Era Medical College and Hospital, Lucknow, Uttar Pradesh, India, over the period of 18 months from June 2019 to December 2020. Institutional Ethical Clearance was obtained (Ref no. ELMCH, Rcell, EC/2019/94, dated-15/05/2019). Total 90 normotensive patients were enrolled for the study. All the patients were informed regarding the risks associated with the procedure and about the anaesthetic agents used in the study. Written and informed consent from each patient was obtained before inclusion in the study.

Inclusion criteria

- Patients scheduled for elective mastoidectomy surgeries
- Age between 18 and 50 years of either sex
- Patients adjudged American Society of Anesthesiologists (ASA) Grade I and II
- Mallampatti airway assessment of Grade I and II.

Exclusion criteria

- Unwilling patients
- Anticipated difficult intubation
- Patients on therapy with α2 adrenergic agonists, β blockers, methyldopa, gabanergic drugs like gabapentin, Monoamine Oxidase (MAO) inhibitors, tricyclic antidepressants, calcium channel blockers and benzodiazepines.
- Patients with history of cardiopulmonary disease or psychiatric illness.

Sample size calculation: Sample size was calculated using the formula from a previously conducted study [9]:

$n=[z(_{1-\alpha/2})]^2\times SD^2/d^2$

Where,

$z(_{1-\alpha/2})$=standard normal deviate for 95% confidence=1.96

SD=Standard deviation of MAP=14 mmHg

d=precision=5%

$n=1.96^2\times 142/5^2$

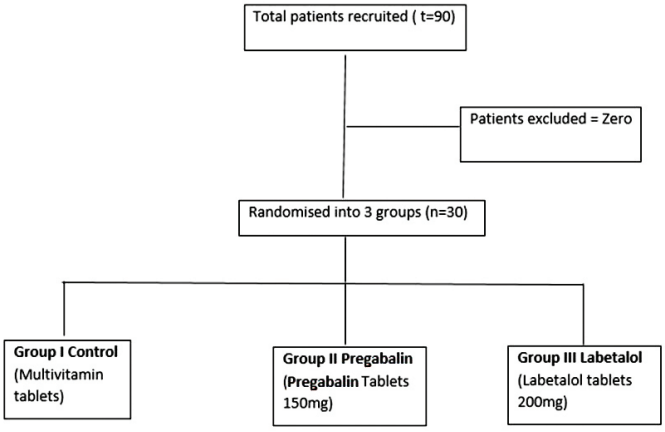
n=30

The sample size obtained was 30 patients in each group. Total of 90 patients were enrolled for this study.

A computer-generated randomisation table was used to allocate patients into three groups.

- Group I (Control) received placebo in form of multivitamin tablets,
- Group II (Pregabalin) received oral pregabalin 150 mg tablet and
- Group III (Labetalol) received tablet labetalol 200 mg.

A staff nurse not participating in the study gave the enrolled participants drugs orally 60 minutes before induction. In the operation theatre, patients were assessed for haemodynamic changes after laryngoscopy and endotracheal intubation by an experienced anaesthesiologist who was blinded to the study drugs [Table/Fig-1].



[Table/Fig-1]: CONSORT flowchart representing study design.

Procedure

A preanaesthetic check-up was done one night before the surgery, patients fasted overnight for 8 hours and preoperative advice was given. Written and informed consent was obtained. On the morning of surgery patients were shifted to the preoperative room and baseline vitals recorded. The study drug was given 60 minutes before induction. After shifting the patient to the operative room, intravenous cannulation was done with an 18 G cannula and ringer lactate solution started. Non invasive blood pressure cuff, pulse oximeter probe, and electrocardiographic leads were attached. A uniform anaesthetic technique was used in all groups which included preoxygenating with 100% oxygen by a face mask for 3 minutes. Induction was done with inj. propofol 2.5 mg/kg. After 30 seconds of induction, relaxation was achieved with inj. vecuronium bromide 0.1 mg/kg. The duration of laryngoscopy and intubation was done by an experienced anaesthetist and controlled to be less than 15 seconds for all patients. Monitoring of vitals was done by an anaesthetist resident, who was blinded to the drug used in each group. Heart rate (BPM) and non invasive SBP, DBP, and MAP (mmHg) were recorded preoperatively (baseline), 60 minutes after administration of study drug, during laryngoscopy, and intubation, and at 1, 2, 5 and 10 minutes after intubation. Maintenance of anaesthesia was carried out using 67% N_20 in 33% oxygen and isoflurane using controlled ventilation and inj. vecuronium 1 mg bolus for muscle relaxation. Intraoperative analgesia was provided with 2 μg/kg fentanyl. After the surgery concluded, residual neuromuscular blockade was reversed using neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg intravenously.

STATISTICAL ANALYSIS

At the end of the study, results were represented as (mean±SD) and percentage changes. The statistical analysis of quantitative data (mean±SD) between the groups was performed using the student's t-test. A p-value <0.05 was considered to be statistically significant. All the analysis was performed using Statistical Package for the Social Sciences (SPSS) statistical package version 20.0 (IBM, Armonk, NY).

RESULTS

The three study groups were statistically comparable for age, body weight, gender [Table/Fig-2] and ASA grade [Table/Fig-3].

Variable		Group I Mean±SD	Group II Mean±SD	Group III Mean±SD	p-value (Student's t-test)
Age (years)		25.53±8.51	24.80±8.19	26.03±9.10	0.856
Weight (kg)		55.97±10.07	61.03±6.59	59.57±9.29	0.077
Gender	Males No. (%)	15 (50.0%)	10 (33.3%)	16 (53.3%)	0.249
	Females No. (%)	15 (50.0%)	20 (66.7%)	14 (46.7%)	

[Table/Fig-2]: Age, weight and gender distribution of cases according to groups.

Physical status	Total (N=90)	Group I (n=30) (n,%)	Group II (n=30) (n,%)	Group III (n=30) (n,%)
ASA I	38	15 (50)	12 (40)	11 (36.7)
ASA II	52	15 (50)	18 (60)	19 (63.3)

[Table/Fig-3]: Intergroup comparison of physical status of study population.
p-value=0.893 (Student's t-test)

The bi-group comparison of heart rate [Table/Fig-4] among the three group pairs showed significant differences at all-time intervals, from after drug administration upto to 10 minutes after induction between Group I and Group II and between Group I and Group III. Between Group II and III significant difference was appreciable at baseline and 60 minutes after drug administration.

Heart rate	Group I vs Group II		Group I vs Group III		Group II vs Group III	
	Mean Diff.	p-value	Mean Diff.	p-value	Mean Diff.	p-value
Baseline	-4.10	0.064	3.40	0.148	7.50	<0.001
60 min after drug administration	-1.83	0.480	5.87	0.001	7.70	<0.001
Induction	10.40	<0.001	10.80	<0.001	0.40	0.977
1 min	7.47	<0.001	8.77	<0.001	1.30	0.779
2 min	10.90	<0.001	10.76	<0.001	-0.13	0.996
5 min	8.03	0.001	6.47	<0.001	-1.56	0.550
10 min	6.03	<0.001	4.27	<0.008	-1.76	0.414

[Table/Fig-4]: Bi-group comparison of heart rates.
(Student's t-test used for calculation of p-value, p-value <0.05 was considered as statistically significant)

The bi-group comparison of SBP [Table/Fig-5] among three group pairs showed significant differences at all the time point found between group I and group II and group I and group III except at baseline. No significant differences were observed in group II and group III except at 2 minutes and 5 minutes after induction.

Systolic Blood Pressure (SBP)	Group I vs Group II		Group I vs Group III		Group II vs Group III	
	Mean Diff.	p-value	Mean Diff.	p-value	Mean Diff.	p-value
Baseline	-5.90	0.016	-2.26	0.524	3.63	0.195
Induction	15.06	<0.001	10.43	<0.001	-4.63	0.057
1 min	17.63	<0.001	13.90	<0.001	-3.73	0.187
2 min	17.03	<0.001	6.73	0.001	-10.30	<0.001
5 min	16.13	<0.001	10.03	<0.001	-6.10	0.003
10 min	12.40	<0.001	12.26	<0.001	-0.13	0.998

[Table/Fig-5]: Bi-group comparison of SBP between group pairs.
(Student's t-test used for calculation of p-value, p-value <0.05 was considered as statistically significant)

The bi-group comparison of DBP [Table/Fig-6] among three group pairs showed significant differences in comparison of Group I and Group II and between Group I and Group III at all time intervals from induction to 5 minutes.

Diastolic Blood Pressure (DBP)	Group I vs Group II		Group I vs Group III		Group II vs Group III	
	Mean Diff.	p-value	Mean Diff.	p-value	Mean Diff.	p-value
Baseline	0.93	0.867	1.63	0.647	0.70	0.923
Induction	17.83	<0.001	6.77	0.006	-11.00	<0.001
1 min	10.80	<0.001	3.87	0.223	-6.93	0.010
2 min	10.20	<0.001	-1.00	0.835	-11.20	<0.001
5 min	11.96	<0.001	3.50	0.179	-8.46	<0.001
10 min	3.60	0.174	6.90	0.002	3.30	0.229

[Table/Fig-6]: Bi-group comparison of Diastolic Blood Pressure (DBP) between group pairs.
(Student's t-test used for calculation of p-value, p-value <0.05 was considered as statistically significant)

The bi-group comparison of MAP [Table/Fig-7] among three group pairs showed statistically significant difference between Group II and Group III from induction to 5 minutes after induction

Mean Arterial Pressure (MAP)	Group I vs Group II		Group I vs Group III		Group II vs Group III	
	Mean Diff.	p-value	Mean Diff.	p-value	Mean Diff.	p-value
Baseline	-4.30	0.028	-1.70	0.558	2.60	0.259
Induction	11.80	<0.001	2.33	0.496	-9.46	<0.001
1 min	5.80	0.026	-1.16	0.855	-6.96	0.006
2 min	4.10	0.072	-1.93	0.547	-6.03	0.004
5 min	4.20	0.052	-0.33	0.981	-4.53	0.033
10 min	3.53	0.094	-0.46	0.958	-4.00	0.050

[Table/Fig-7]: Bi-group comparison of MAP between group pairs.
(Student's t-test used for calculation of p-value, p-value <0.05 was considered as statistically significant)

DISCUSSION

This randomised control study was conducted to compare the efficacy of preoperative oral pregabalin and oral labetalol in attenuating haemodynamic responses to laryngoscopy and intubation.

On evaluating the intra-group differences in heart rate oral pregabalin showed slightly better control of heart rate than oral labetalol, in the pre-intubation period. Pregabalin being a gabapentenoid compound acts on Central Nervous System (CNS) to cause sedation. This was appreciated by the fact that one hour after being administered the drug, group II (pregabalin) showed the most reduction in heart rate amongst the three groups. This can be explained by the calm and relaxed state of the patients owing to the sedative effect of pregabalin. However, the difference in attenuation of heart rate postintubation and the rest of the observed intervals during surgery was not statistically different between pregabalin and labetalol, although both the drugs showed significantly better attenuation in heart rate than the control group.

Observations to the similar effect were also made by various studies. Reddy MS and Murari N conducted a study to observe the efficacy of pregabalin premedication 90 minutes before surgery in attenuating the adverse haemodynamic response to laryngoscopy and tracheal intubation, which showed that all haemodynamic parameters (SBP, DBP, MAP) were effectively controlled by pregabalin but the effect on heart rate was minimal [10]. Bhandari G et al., compared oral pregabalin with placebo in a study to investigate the effect of pregabalin premedication on haemodynamic responses to laryngoscopy and intubation [11]. In their study, they concluded that oral pregabalin premedication at a dose of 150 mg one hour before surgery attenuates pressor response associated with laryngoscopy and endotracheal intubation but not the tachycardia significantly. Rastogi B et al., conducted a study in 90 normotensive ASA grade I and II patients of either gender aged 24-56 years, randomised into three treatment groups of 30 patients each [12]. Group I received oral placebo, Group II oral pregabalin 75 mg and Group III oral pregabalin 150 mg 1 hour prior to induction. They noticed that preoperative sedation levels were higher with pregabalin premedication. Significant increase in heart rate and MAP was observed in Groups I and II after airway instrumentation, while statistically significant attenuation of MAP was seen in Group III. No significant decrease in heart rate was observed in any group. This showed that pregabalin has a minimal role in attenuation of heart rate during and postintubation.

Although i.v. labetalol, administered just before intubation has been shown to offer attenuation of all haemodynamic parameters including heart rate [6,13], studies showing the same with oral labetalol are limited. Similar to the present study Patta S et al., conducted a study to compare labetalol and clonidine as premedication to attenuate haemodynamic changes to laparoscopy through oral route [7]. The study included 60 adult patients of both sexes of

ASA grade I and II divided randomly into two groups of 30 each, Group L and Group C. Group L were given tab. labetalol 200 mg orally 60-90 minutes before induction. Group C was given tab. clonidine 300 µg orally 60-90 minutes before induction. The degree of attenuation of haemodynamic changes during laparoscopic surgeries was then compared. They concluded that oral clonidine showed better attenuation of haemodynamic changes than oral labetalol and that oral labetalol showed minimum control of stabilising all haemodynamic parameters including heart rate. In the present study, the reduction of heart rate was least appreciated in the control group.

Aside from heart rate, for SBP, DBP, and MAP, oral pregabalin showed a significantly greater attenuation of these haemodynamic parameters than oral labetalol. As expected, the control group was least effective in attenuating these responses.

The reason why oral pregabalin proved better at stabilising haemodynamic parameters than oral labetalol in the present study could have been due to the nature of the drugs and timing before induction at which the drugs were administered. Labetalol is lipid-soluble. It undergoes considerable hepatic first-pass metabolism and has a bioavailability of approximately 25% [4,5]. It reaches peak plasma concentrations generally within 2-3 hours [4]. Pregabalin is water soluble with a bioavailability of over 90% and reaches peak plasma concentrations generally within 1-1.5 hours [3]. In this study, the drugs were prescribed 1 hour before induction. This might have resulted in pregabalin reaching peak plasma concentrations, leading to better attenuation of haemodynamic responses to intubation.

In the present study, no toxic side-effect of either of the two drugs (viz., nausea, hypersensitivity, vomiting, headache) was noted. No adverse haemodynamic event like supine hypotension was also noted. This might be probably attributable to the low dose and short duration of observation in our study. Any side-effects, if encountered, would have been managed accordingly.

Limitation(s)

Since oral pregabalin is known to cause sedation, a sedation score could have been implemented in the study to better evaluate sedation in patients. Intra and postoperative analgesic requirements could also have been noted. Further studies incorporating the above factors and involving different doses of the drugs and administered at different times are needed to better compare these two drugs.

CONCLUSION(S)

The present study was conducted to compare the relative efficacy of pregabalin and labetalol for attenuation of pressor responses during laryngoscopy and tracheal intubation. The study showed that though both pregabalin and labetalol were effective in controlling postintubation haemodynamic changes, attenuation of all immediate postintubation haemodynamic changes except heart rate was more effective with pregabalin as compared to labetalol. The difference in attenuation of heart rate was not significant between pregabalin and labetalol.

REFERENCES

[1] Gupta K, Sharma D, Gupta PK. Oral premedication with pregabalin or clonidine for haemodynamic stability during laryngoscopy and laparoscopic cholecystectomy: A comparative evaluation. Saudi J Anaesth. 2011;5:179-84.
[2] Gurulingappa, Aleem MA, Awati MN, Adarsh S. Attenuation of cardiovascular responses to direct laryngoscopy and intubation-a comparative study between i.v. bolus fentanyl, lignocaine and placebo(NS). J Clin Diagn Res. 2012;6(10):1749-52.
[3] Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia. 2004;45:13-18.
[4] MacCarthy EP, Bloomfield SS. Labetalol: A review of its pharmacology, pharmacokinetics, clinical uses and adverse effects. Pharmacotherapy. 1983;3(4):193-219.
[5] Abdullah A, Yusof M. Labetalol: A brief current review. Pharmacophore. 2019;10(6):50-56.
[6] Singh SP, Quadir A, Malhotra P. Comparison of esmolol and labetalol, in low doses, for attenuation of sympathomimetic response to laryngoscopy and intubation. Saudi J Anaesth. 2010;4(3):163-68.
[7] Patta S, Karem PK, Bevara KC, Satyanarayana A. Comparison between tab. clonidine and tab. labetalol as oral premedication in attenuation of haemodynamic changes during laparoscopic surgery: A randomised double blind study. Journal of Evidence Based Medicine and Healthcare. 2016;3:606-13.
[8] Sundar AS, Kodali R, Sulaiman S, Ravullapalli H, Karthekeyan R, Vakamudi M. The effects of preemptive pregabalin on attenuation of stress response to endotracheal intubation and opioid-sparing effect in patients undergoing off-pump coronary artery bypass grafting. Ann Card Anaesth. 2012;15(1):18-25.
[9] Singh D, Yadav JS, Jamuda BK, Singh P. Oral pregabalin as premedication on anxiolysis and stress response to laryngoscopy and endotracheal intubation in patients undergoing laparoscopic cholecystectomy: A randomised double-blind study. Anaesth Essays Res. 2019;13(1):97-104.
[10] Reddy MS, Murari N. Efficacy of pregabalin premedication prior to surgery in attenuating the adverse haemodynamic response to laryngoscopy and tracheal intubation. International Journal of Advances in Medicine. 2019;6(3):769-73.
[11] Bhandari G, Mitra S, Shahi KN, Rani A, Chauhan A. Pre-emptive use of oral pregabalin attenuates the pressor response of laryngoscopy and endotracheal intubation: A double blind randomised placebo controlled study. Annals of International Medical and Dental Research. 2016;2(3):110-14.
[12] Rastogi B, Gupta K, Gupta PK, Agarwal S, Jain M, Chauhan H. Oral pregabalin premedication for attenuation of haemodynamic pressor response of airway instrumentation during general anaesthesia: A dose response study. Indian J Anaesth. 2012;56(1):49-54. Doi: 10.4103/0019-5049.93344. PMID: 22529420; PMCID: PMC3327071.
[13] Ratnani E, Sanjeev OP, Singh A, Tripathi M, Chourasia HK. A comparative study of intravenous esmolol, labetalol and lignocaine in low doses for attenuation of sympathomimetic responses to laryngoscopy and endotracheal intubation. Anaesth Essays Res. 2017;11(3):745-50. Doi: 10.4103/aer.AER_9_17. PMID: 28928581; PMCID: PMC5594800.

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