**Original article:**

**Attenuation of cardiovascular responses following laryngoscopy and tracheal intubation: comparative assessment of Dexmedetomidine and Pregabalin**

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**ABSTRACT**

**Background:** Laryngoscopy and tracheal intubation are noxious stimuli that evoke a transient but marked sympathetic response manifesting as increase in heart rate, blood pressure & arrythmia. . Dexmedetomidine and pregabalin are relatively newer drugs which have been used for this purpose. The present study evaluated and compared the effects of these drugs for attenuation of hemodynamic pressor response by airway instrumentation.

**Methods :** A total of 60 normotensive adult consented patients for elective surgery aged 18-65 years, ASA grade I, of both gender were randomised into two groups of 30 patients each. Patients in Group D received dexmedetomidine by intravenous infusion at rate of 0.6μg/kg over 10 minutes, followed by endotracheal intubation after an interval of another 10 minutes. Patients in Group P received 150 mg of capsule pregabalin orally one hour before endotracheal intubation. Anaesthetic technique was standardized and both group were assessed and compared for pre-operative hemodynamic values, hemodynamic changes after the premedication, before and after intubation as well as after laryngoscopy and intubation at 1, 2, 3, 4 and 5 minutes.

**Results:** The maximum increase from baseline was seen at one minute interval. The increase in heart rate in Dexmedetomidine group (10.22%) was significantly less than Pregabalin group (32.30%). Changes in systolic blood pressure after intubation and laryngoscopy were significantly lower in Dexmedetomidine group (11.61%) as compared to Pregabalin group (26.36%).. The rise in diastolic blood pressure was not significantly prevented in both groups. The MAP was significantly lower in group D following intubation.

**Conclusion :** Dexmedetomidine infusion in the dose of 0.6 μg/kg given preoperatively under the present study design condition attenuates the tachycardia and pressor responses associated with laryngoscopy and intubation more than pregabalin in the dose of 150 mg administered orally.

**Introduction**

Intubation of the trachea is an essential step for administration of general anaesthesia to a patient undergoing surgical procedure. Laryngoscopy and tracheal intubation are noxious stimuli that evoke a transient but marked sympathetic response manifesting as increase in heart rate, blood pressure & arrhythmia. These physiological changes are well tolerated by healthy individuals. However these changes may be detrimental or even fatal in patients with pre-existing coronary artery disease, hypertension, cerebrovascular disease, intracranial aneurysm, valvular heart disease. The sympathetic response may be associated with acute left ventricular failure1, ischaemic ECG changes2, and ruptured cerebral aneurysm1. As today more and more patients with cardiovascular disorders are presenting themselves for surgery, anaesthesiologists are in search of more safe and efficient drug which can minimise cardiovascular response to the laryngoscopy and tracheal intubation.

Deepening of anesthesia, lidocaine spray, sodium nitroprusside, opioids, α blockers, I.V lignocaine , nitroglycerine ointment and oral clonidine4 have been traditionally used as preoperative medication to eliminate or to attenuate the stress response to laryngoscopy and intubation.

Dexmedetomidine and pregabalin are relatively newer drugs which have been used for this purpose. Dexmedetomidine, is a highly selective α-2-adrenergic agonist, which increases perioperative cardiovascular stability in healthy adults. The intraoperative use of dexmedetomidine may increase hemodynamic stability because of attenuation of the stress-induced sympathoadrenal responses to intubation, during surgery and during emergence from anaesthesia6.. For adult patients, dexmedetomidine is administered by a loading intravenous infusion of 0.5-1 μg/kg over 10 minutes, The effect appears in 5-10 min, and is reduced in 30-60 min..

Pregabalin, a gabapentinoid compound, is described structurally as (s)-3- aminomethyl-5-methylhexanoic acid. It acts by decreasing the synthesis of neurotransmitter glutamate to act on central nervous system and possesses analgesic, anticonvulsant and anxiolytic activity and is effective in preventing neuropathic component of acute nociceptive pain of surgery7.,. It has also been shown to attenuate cardiovascular responseto laryngoscopy and intubation8.

The present study was designed as prospective randomized study to evaluate and compare the efficacy of dexmedetomidine and pregabalin premedication for attenuation of haemodynamic pressor response of laryngoscopy and intubation with perioperarative haemodynamic stability at the Department of Anaesthesiology of Northern Railway Central Hospital, New Delhi.

**Material and methods**

This study was randomised prospective comparative study. A total of 60 normotensive adult consented patients were taken after clearance from ethical committee, the study was conducted between April 2012 to May 2013.Patients posted for elective surgery aged 18-65 years, , of both gender were randomised into two groups of 30 patients each..Patients with anticipated difficult intubation, Chronic Obstructive Pulmonary Disease (COPD) , hepatic disease, renal disease, seizure disorder, pregnancy or lactation, antihypertensive medication and any history of allergy to pregabalin or dexmedetomidine were excluded from study. When duration of laryngoscopy exceed 15 seconds or second attempt for intubation was needed those patients were also excluded from study.

After thorough pre-anaesthetic evaluation, patients were randomly allocated (by picking of chits) to two groups of 30 patients each. All patients were given tablet Alprazolam 0.25mg at the night before surgery and 0.25 mg in morning on day of surgery. Patients in Group D received dexmedetomidine by intravenous infusion at rate of 0.6μg/kg over 10 minutes, followed by endotracheal intubation after an interval of another 10 minutes. Patients in Group P received 150 mg of capsule pregabalin orally one hour before endotracheal intubation. The patients in Group P also received intravenous infusion of normal saline of equal volume at same rate as in Group D so as to avoid bias between the two groups.

Before given the drug, monitors were attached and baseline (preoperative) heart rate by ECG, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure by continuous non invasive arterial pressure (CNAP) were recorded, using multiparameter monitor (Infinity C700 Drager Fabius Plus )

A crystalloid intravenous infusion of 6-8mL/Kg was started. After pre-oxygenation for 3 minutes with 100% oxygen, anaesthesia was induced with injection thiopentone till dissappearance of eye lash reflex. The direct laryngoscopy and intubation was facilitated with rocuronium( 0.6 mg/Kg) after 90 seconds. It was similar in all patients. During the initial five minutes of intubation, any drug which could affect blood pressure was not administered through any route and anaesthesia was maintained by oxygen and nitrous oxide in 1:2 ratio and surgery was not started. Any possibility of awareness was ruled out, since it is generally believed that administration of at least 0.5 minimum alveolar concentration of any volatile anaesthetic agent should prevent awareness during GA9.

After 5 minutes of intubation anaesthesia was maintained with isoflurane and nitrous oxide 60% in oxygen and intermittent relaxant

Intraoperatively, the heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure using CNAP and oxygen saturation (SpO2) were continuously monitored. The time scheduled for measurement of above parameter was as follows :

1. Before administration of test drug (preoperative value).
2. Before induction of anaesthesia and after administration of test drug (preinduction value).
3. Immediately after laryngoscopy ( 0 minute)
4. At interval of 1, 2, 3, 4 and 5 minutes following intubation.

Patients were observed for complications like hypotension, hypertension, arrhythmias, hypoxemia and bronchospasm, and treated as required according to standard guidelines. Tachycardia was defined as heart rate greater than 100 beats/min and hypertension when systolic blood pressure was more than 180 mmHg. Hypotension was defined as fall in mean arterial pressure by more than 20% from baseline. Bradycardia was defined as reduction in heart rate below 60 beats/min.

**Statistical Analysis**

The sample size was decided in consultation with the statistician and was based on initial pilot observations, indicating 25-27 patients should be included in both groups in order to ensure a power of 0.80 for detecting clinically meaningful attenuation of heart rate and pressor response by maximum rise of 10-20%. Assuming a 10% drop out rate, the final sample size was set at 60 patients, which would permit atype I error of alfa =0.05, with type II error of beta = 0.5 and power of study 0.8.

 Statistical analysis was conducted with Statistical Package for the Social Sciences (SPSS) statistical software version 15.0 and Microsoft excel by using Chi-Square test, paired and unpaired student’s t-test. The results were expressed as Mean ± SD. P < 0.05 was regarded as statistically significant, P < 0.001 was taken as highly significant, and P > 0.05 was regarded as non significant. The failure rate of drug was defined as > 30% increase in hemodynamic parameters from the baseline values.

**Results:**

The two study groups were comparable with regard to age, sex and weight table-1. Following laryngoscopy and intubation there were increase in heart rate in both groups.The maximum increase from baseline was seen at one minute interval. The increase in heart rate in Dexmedetomidine group (10.22%) was significantly less than Pregabalin group(32.30%). [Table2]

Changes in the systolic blood pressure after intubation and laryngoscopy were significantly lower in dexmedetomidine group (11.61%) as compared to pregabalin group (26.36%)

 Attenuation of systolic blood pressure was more with dexmedetomidine at all recorded time intervals. Although there were significant difference in attenuation of systolic blood pressure found at 1 minute, their effects are comparable at 0, 2, and 3 minutes. At 4 minute Group D showed statistically significant lowering of SBP below the preoperative values as comparable to Group P and this lowering was comparable at 5 minute. [ Table 3]

The rise in diastolic blood pressure was not significantly prevented in both groups. The maximum rise from baseline seen at 1 minute by 24.47% and 31.91% in Group D and P respectively, the difference was statistically significant. Although Group D shows significantly lower values than Group P at all time intervals, these values are comparable at 0, 2, 3, 4 and 5 minutes. [ Table 4]

The maximum rise in MAP found at 1 minute after intubation were 18.71% and 31.09% in Group D and Group P respectively, which was statistically significantly less in dexmedetomidine group. Both Groups were comparable at 0, 2, 3, 4 and 5 minutes. [ Table 5]

Clinically significant respiratory depression was not seen in any study group. A decreased

amount of Thiopentone requirement for induction of anaesthesia in Dexmedetomidine group

 as compared to Pregabalin group was observed. Although there was no differences among

 the both groups with respect to awakening and recovery time,the two patients in Pregabalin

 group had excessive postoperative somnolence.

Table 1 : Demographic profile of patient.

|  |  |  |  |
| --- | --- | --- | --- |
| Demographic profile | Group D | Group P | P- Value |
| Age | 39.03 ± 13.74 | 44.57 ± 12.16 | 0.5202 |
| Sex M/F | 4/26 | 8/22 | 0.09835 |
| Weight | 59.97 ±12.12 | 62.93 ±6.12 | 0.11819 |
|  |  |  |  |

Table 2: Mean Heart Rate in the two groups at the stated intervals and their statistical comparison between two groups

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|   | Heart Rate | Preop | Preind | 0min | 1min | 2min | 3min | 4min | 5min |
| Dexmede-tomidine | Mean | 87.70 | 80.93 | 93.53 | 96.67 | 93.27 | 93.33 | 90.80 | 88.47 |
| SD | 16.36 | 12.60 | 13.92 | 15.69 | 15.64 | 15.15 | 15.08 | 14.88 |
| Pregablin | Mean | 81.63 | 86.77 | 104.37 | 108.00 | 105.60 | 103.57 | 97.67 | 94.67 |
| SD | 10.18 | 12.77 | 14.63 | 13.89 | 15.48 | 16.33 | 14.69 | 16.18 |
| P-valueDexmedetomidinevs.Pregablin | 0.04493 | 0.04008 | 0.00236 | 0.00221 | 0.00163 | 0.00732 | 0.03965 | 0.06391 |

Table 3 : Mean Systolic Blood Pressure at the selected recording times and their statistical comparison between two groups.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|   | Systolic BP | Preop | Preind | 0min | 1min | 2min | 3min | 4min | 5min |
| Dexmede--tomidine | Mean | 128.77 | 110.37 | 135.47 | 143.73 | 136.27 | 128.23 | 118.83 | 117.20 |
| SD | 15.97 | 17.48 | 28.52 | 22.05 | 20.80 | 19.91 | 19.20 | 20.01 |
| Pregabalin | Mean | 126.80 | 122.27 | 140.53 | 160.23 | 144.73 | 136.30 | 127.17 | 122.67 |
| SD | 13.62 | 14.38 | 16.14 | 20.62 | 24.10 | 18.76 | 15.58 | 15.92 |
| P-value Dexmedetomidine vs.Pregablin | 0.30488 | 0.00278 | 0.20027 | 0.00202 | 0.07527 | 0.05583 | 0.03497 | 0.12317 |

Table 4: Mean Diastolic Blood Pressure at the selected time intervals and their statistical comparison between two groups.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|   | Diastolic BP | Preop | Preind | 0min | 1min | 2min | 3min | 4min | 5min |
| Dexmede-tomidine | Mean | 79.40 | 71.07 | 91.57 | 98.83 | 92.40 | 86.37 | 79.80 | 76.40 |
| SD | 7.44 | 12.29 | 20.23 | 12.55 | 10.80 | 9.46 | 11.77 | 11.64 |
| Pregabalin | Mean | 78.10 | 79.73 | 94.43 | 105.37 | 94.67 | 89.37 | 83.50 | 80.30 |
| SD | 9.56 | 8.25 | 11.19 | 14.39 | 13.38 | 10.51 | 9.62 | 9.08 |
| P-value Dexmedetomidine vs.Pregablin | 0.27948 | 0.00110 | 0.24989 | 0.03299 | 0.23661 | 0.12502 | 0.09386 | 0.07667 |

Table 5 : Mean of Mean Arterial Pressure at the selected time intervals and their statistical comparison between two groups

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|   | Mean Arterial Pressure | Preop | Preind | 0min | 1min | 2min | 3min | 4min | 5min |
| Dexmede-tomidine | Mean | 95.86 | 84.17 | 106.20 | 113.80 | 107.02 | 100.32 | 92.81 | 90.00 |
| SD | 9.47 | 13.29 | 21.85 | 14.35 | 13.29 | 12.32 | 13.61 | 13.85 |
| Pregablin | Mean | 94.33 | 93.91 | 109.80 | 123.66 | 111.36 | 105.01 | 98.06 | 94.42 |
| SD | 9.57 | 8.72 | 11.19 | 14.31 | 16.33 | 12.35 | 10.56 | 10.67 |
| P-value Dexmedetomidine  vs.Pregablin | 0.26910 | 0.00070 | 0.21255 | 0.00500 | 0.13214 | 0.07314 | 0.05042 | 0.08563 |

**Discussion**

The present study was undertaken to assess the role of intravenous Dexmedetomidine and oral Pregabalin in attenuating the pressor response to laryngoscopy and intubation. The significant attenuation of hemodynamic pressor response was observed in intravenous Dexmedetomidine group as compared to oral Pregabalin.

Jakola ML, et al9 found that the maximal blood pressure and heart rate in the group which had received 0.6 μg/kg of dexmedetomidine before anaesthesia, were significantly lower than those of control group. Suparto et al10 found that dexmedetomidine in dose of 1 μg / kg / hr, attenuates pressor response to laryngoscopy and intubation but adverse events like bradycardia and hypotension were also noted in their study. Therefore they recommended a lower dose of dexmedetomidine to decrease the adverse effects. Hall et al11 observed biphasic cardiovascular changes, where blood pressure initially decreased followed by a momentary rise in blood pressure for 10 min after administration of dexmedetomidine, occurred after bolus injection of dexmedetomidine.. Therefore, in the present study, the dose of dexmedetomidine has been chosen as 0.6 μg/ kg and given as a slow intravenous infusion over 10 minute and thereafter the patiients were induced after another 10 minutes.

Rastogi B. et al13 and Gupta K. et al7,8 found that oral pregabalin when given in dose of 150 mg per oral one hour prior to surgery is effective in attenuation of the deleterious hemodynamic responses of laryngoscopy and intubation. White PF et a14  in a study reported difficulty in regaining consciousness in PACU in a greater percentage of patients who had received oral pregabalin in a dose of 300 mg and also had complaints such as dizziness (or light-headedness). Hall et al12 suggested that pregabalin 300 mg per oral had a longer duration of analgesia but reported more frequent adverse effects like excessive sleepiness and dizziness. Therefore in our study dose of pregabalin was taken as 150 mg and given per orally one hour prior to beginning of surgery. After premedication with tablet alprazolam but before administration of test drug, the baseline (preoperative) heart rate recorded in the two groups were : Group D 87.7 ± 16.36, Group P 81.63 ± 10.18. ( Table 2).

The preoperative values for heart rate show a significant difference between Group D and Group P, being higher in Group D. This can be attributed to preoperative anxiety as preoperative pulse rate was taken in the operating room in Group D while in Group P it was taken in the ward before administration of the drug. As patients tend to remain anxious in operating room than in the ward. After giving the test drug and before induction, the HR decreased in Group D (by 7.7%) while increased in Group P (by 6.29%) (Table 2). Dexmedetomidine infusion causes more sedation and anxiolysis than pregabalin. White PF, et al13 concluded that pregabalin (75–300 mg orally) failed to produce a significant anxiolytic effect when administered for preoperative medication, Our findings are almost similar to findings of Rao SH, et al14 and Bajwa SJS, et al15 who found significant reduction in heart rate following the loading dose of dexmedetomidine (12.31%).

Gupta K, et al7,8, Rastogi B, et al12 did not find any significant difference in HR values before and after premedication with pregabalin in dose of 150 mg. This finding is similar to our study. Following laryngoscopy (0 minute), there was an increase in heart rate in both groups (Table 2). In the Dexmedetomidine group (Group D), the mean HR increased to 93.53 ± 13.92 (7.4%) which was statistically significant (Table 1). This finding is in accordance with Suparto et al10 who also found an increase in HR following laryngoscopy.

. This is in accordance with the study done by Rastogi B, et al12, using oral pregabalin 75mg and 150 mg who also found significant increase in heart rate in both groups immediately after laryngoscopy.

 In our study the readings of the heart rate recorded a sharp increase following endotracheal intubation, with the readings highest at 1 minute interval in both groups (Table 2). In Group D the heart rate increased to a mean of 96.67 ± 15.69, at 1 minute which was statistically highly significant (P<0.001). Thereafter, the heart rate showed a downward trend and by 4 minutes, it was statistically comparable with the preoperative value. Our finding is in accordance with Kayamak C, et al16, Jakola ML, et al9 and Bajwa SJS, et al15. But our finding differ from Sulaiman S, et a17 (0.5μg/kg) who found statistically significant decrease in heart rate at all time intervals, probably because their study patients continued β blocker on day of surgery.

In Group P the mean heart rate at 1 minute interval was 108.00 ± 13.89 beats per minute which was an increase of 26.37 (P < 0.001). Nearly 67% patients in this group at one minute interval showed a heart rate of more than 100 beats/ minute.., No statistically significant attenuation of heart rate was observed in pregabalin group. This finding is in accordance with the findings of Gupta K et al7and Rastogi B et a12.

Therefore dexmedetomidine though, not completely attenuating the heart rate, is better than pregabalin in maintaining a lower heart rate following intubation. The preoperative mean Systolic blood pressure recorded in the both groups were stastically comparable table(3) After giving the test drug the systolic blood pressure decreased in both groups. The decrease in SBP in Group D is by 14.28% which was found to be statistically highly significant (Table 3). The finding of Group D is in accordance with Jakola ML, et al10 and Suparto et al11, as they also observed decrease in SBP to be statistically highly significant after administration of the drug. The decrease in SBP in Group P was only by 3.5%, which is almost equal to preoperative value. The finding of pregabalin group is in accordance with Sundar AS, et al18 as they found that there was no significant difference in SBP values before and after premedication.

Following laryngoscopy and. intubation, the highest rise in mean SBP in both the groups,was seen at 1 minute In Group D, SBP raised to 143.73 ± 22.05 mm Hg, i.e. by 11.61% over the preoperative value. The mean SBP reached to preoperative value by 3 minutes. Our finding is in accordance with Lee JH, et 19, they found maximum rise in SBP was at 1 minute and increased from preoperative value by 14.6%.

In Group P, the maximum rise in SBP was upto 160.23 ± 20.62 mm Hg, i.e. by 26.36% over preoperative value which was found at 1 minute. The raised SBP returned to preoperative value by 4 minutes. These findings are contrary to findings of Sundar AS et al18, where they found significant decrease in SBP at 1 minute of intubation., the study was done on the patients scheduled for bypass surgery who were on antihypertensive drugs and t also received fentanyl during induction.

In intergroup comparison between Group D and Group P, the mean SBP was significantly lower in Group D following intubation (Table 3). The readings were statistically significant (P< 0.05) at 1 minute interval and not significant (P> 0.05) at 2, 3 and 5 minutes.

After giving the test drug but, immediately before induction (preinduction), in Group D, mean Dastolic blood pressure decreased to 71.07 (i.e. by 10.49%), which is statistically significant (Table 4). The finding is in accordance with Suparto et al11, as they found 11% decrease in DBP before laryngoscopy. The DBP in Group P was nearly equal to preoperative value (Table 4). The finding of pregabalin group is in accordance with Sundar AS, et al18,. Following laryngoscopy and. intubation, the highest rise in mean DBP in both the groups,was seen at 1 minute. In Group D, DBP increased to 98.83 ± 12.55 mm Hg, (i.e. by 24.47 %) over the preoperative value. The mean DBP returned back to preoperative value by 4 minutes. these findings are contrary to the findings of Lee JH, et al19. They used dexmedetomidine infusion at 1 μg/kg and found maximum rise in DBP by 15.7% was at 1 minute. They also found bradycardia very frequently, whereas in our study bradycardia not seen. The difference might have been due to the use of higher drug dose.

In Group P, the maximum rise in DBP was to 105.37 ± 14.39 mm Hg, i.e. by 31.91% over preoperative value was found at 1 minute (Table 3). The raised DBP did not return to preoperative value by 5 minutes. These findings are contrary to findings of Sundar AS, et al18 because the study population selected by them were on antihypertensive drugs .

In intergroup comparison between Group D and Group P, the mean DBP were significantly lower in Group D following intubation (Table 4). The readings were statistically significant (P< 0.05) at 1 minute interval and not significant (P> 0.05) at 2, 3, 4 and 5 minutes of intubation.

 Mean Arterial Pressure before administration of the test drug (preoperative) was 95.86 ± 9.47 mmHg in Group D and 94.33 ± 9.57 mmHg in Group P.

After giving the test drug but immediately before induction (preinduction), in Group D, mean MAP decreased to 84.17 (i.e. by 12 %), which is statistically significant (Table 5).The finding is in accordance with Bajwa SJS, et al16, as they found 10-15% decrease in MAP before laryngoscopy. The MAP in Group P was nearly equal to preoperative value (Table5). The findings of pregabalin group is in accordance with Sundar AS, et 18, Rastogi B, et a13 and Gupta K, et al7,8as they found there was no significant difference in mean MAP before and after premedication. Following laryngoscopy and. intubation, the highest rise in mean MAP in both the groups,was seen at 1 minute. In Group D, MAP maximally increased to 113.80 ± 14.35 mmHg, i.e. by 18.71 % over the preoperative value. . The mean MAP returned back to preoperative value by 4 minutes and is comparative to preoperative value. In Group P, the maximum rise in MAP to 123.66 ± 14.31 mm Hg, i.e. by 31.09% over preoperative value was found at 1 minute (Table 5) The raised MAP returned to preoperative value by 5 minutes of intubation. These findings are not in accordance with Gupta K, et al7,8 who found maximum rise in MAP only by 15.26% and MAP did not return to preoperative value even after 5 minutes. They found lower rise in MAP, may be because they use fentanyl during premedication and propofol as induction agent.

In the intergroup comparison between Group D and Group P, the mean MAP was significantly lower in Group D following intubation (Table 5). The readings were statistically significant (P< 0.05) only at 1 minute interval and comparable (P> 0.05) at 2, 3, 4 and 5 minutes after intubation. groups.

**Conclusion:**

 Dexmedetomidine infusion in the dose of 0.6 μg/kg given preoperatively under the present study design condition attenuates the tachycardia and pressor responses associated with laryngoscopy and intubation more than pregabalin in the dose of 150 mg administered orally.

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For any images presented appropriate consent has been obtained from the subjects: NA

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