Dexmedetomidine as an adjunct to anaesthetic induction to attenuate haemodynamic responses to Endotracheal Intubation

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Abstract
Introduction: The hemodynamic responses to endotracheal intubation (EI) may impose myocardial ischemia, infarction (MI); arrhythmias or precipitate cardiac failure. Dexmedetomidine, which is a D-isomer of medetomidine is more specific for alpha 2 adrenergic receptor and shorter acting than clonidine. As studies to explore the property of dexmedetomodine for attenuation of haemodynamic responses to EI are only few, this study was an attempt to assess the efficacy and safety of dexmedetomidine for the same.

Aim and Objectives: To assess the efficacy of a single preoperative dose of intravenous dexmedetomidine in attenuating the haemodynamic responses to EI.

Materials and Method: The study design was prospective, interventional randomised placebo controlled clinical trial. Each and every patient who fulfilled the eligibility criteria was randomly assigned to one of the two groups, Group C (Control) or Group D (Dexmedetomidine), using a computer generated random number table. Participants of group C received 20 ml of normal saline over 15 minutes and of group D received dexmedetomidine 0.5µg/kg diluted in normal saline to make 20 ml over 15 minutes through a syringe pump.

Results: There was statistically significant rise in the mean heart rate in Group C, during EI from 82.82 ± 13.37 to 115.86 ± 13.12 (p<0.001). In Group D, there was a decrease in mean heart rate at preinduction from basal value of 86.74 ± 15.37 to 76.00 ± 14.77 (p<0.001). The mean heart rate during EI (I) and also at one minute after intubation came to near basal level 87.82 ± 15.41 (p>0.05). Similar results were for systolic arterial pressure, diastolic arterial pressure, mean arterial pressure and rate pressure product.

Conclusion: From the present study, it is concluded that pretreatment with dexmedetomidine 0.5µg/kg attenuated the sympathoadrenal response to laryngoscopy and endotracheal intubation effectively, but could not obtund it completely. It was also inferred that tachycardiac response was better attenuated than pressure response.

Keywords: Haemodynamic responses, Endotracheal intubation, Dexmedetomidine, Sympathoadrenal responses, Myocardial ischaemia

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Introduction
Laryngoscopy and Endotracheal Intubation (EI) are the most painful stimulus during perioperative period. Although this procedure is completed within very brief period, it imposes great haemodynamic perturbations. The hemodynamic responses to endotracheal intubation (EI) may impose myocardial ischemia, infarction (MI); arrhythmias or precipitate cardiac failure.(1)

Various tricks and drugs have been used to attenuate the haemodynamic responses to EI. And many of them are used in day to day practice but with limited efficacy. As a result the search of an ideal drug is continued. A novel drug from the family of alpha-2 adrenergic agonist, Dexmedetomidine has been introduced in the practice of anaesthesia for different indications. It is a D-isomer of medetomidine and is more specific for alpha 2 adrenergic receptor and shorter acting than clonidine. In recent studies, this drug has been shown to have clinically significant effects on anaesthetic requirements.(2,3,4,5,6.7)

By virtue of its sympatholytic action, dexmedetomidine decreases heart rate and blood pressure. So we hypothesized that this drug can be used to attenuate the sympathoadrenal responses to endotracheal intubation. For this very purpose this study was designed to explore the efficacy and safety of dexmedetomidine for attenuation of haemodynamic responses to EI.

Aim and Objectives
The aim of this study was to assess the efficacy of a single preoperative dose of intravenous dexmedetomidine in attenuating the haemodynamic responses to EI.

The primary objectives were to assess:
1. The changes in heart rate, systolic, diastolic & mean arterial pressures and rate pressure product during and after endotracheal intubation.
2. To assess the effect of dexmedetomidine in attenuating these cardiovascular responses.
Materials and Method

Study design: The study was designed as prospective, interventional, randomised, placebo controlled clinical trial. This study was conducted at the Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna during a period of one year and four months between 2011-2013. Patients reporting to preanaesthetic clinic for preanaesthetic evaluation for proposed gastrointestinal surgeries were screened for recruitment in the study.

Sample Size: Fifty patients in each group were included. The quantitative estimate of intravenous dexmedetomidine in attenuating haemodynamic responses to laryngoscopy and endotracheal intubation was not available. So the results of pilot study was used to calculate the sample size. Mac Whiteni test was applied with taking alpha error 5% and power of study 95%. Sample size calculated was 30 in each group. Then it was multiplied by 1.5 to remove sampling error. So it came to 45 in each group. Further considering loss of follow up 5 more patients were added in each group.

After getting approval of institute ethical committee 100 consecutive patients of either sex, ASA class I or II and age group 20-50 years scheduled for different abdominal surgeries under general anaesthesia and willing to give consent were included in the study. A written informed consent was obtained from all the participants. Patient’s refusal, emergency surgery, any comorbid of ASA grade III and above, morbid obesity (BMI >30 kg/m²), pregnant & lactating women, predicted difficult intubation, Intubation attempt lasting longer than 20 seconds were exclusion criteria for this study.

Participants were randomly assigned to one of the two groups, Group C (Control) or Group D (Dexmedetomidine), using a computer generated random number table. All patients were pre-medicated with oral tablet lorazepam 1 mg and pantoprazole 40mg night before surgery. After wheeling into operation room ECG, Pulse oximetry and non-invasive blood pressure monitoring was started.

Intervention Plan:
Group C: Participants of this group received 20 ml of normal saline infused over 5 minutes through a syringe pump.
Group D: Participants of this group received dexmedetomidine 0.5µg/kg diluted in normal saline to make 20 ml through infusion over 15 minutes by a syringe pump.

After 10 minutes of starting infusion anaesthesia was induced with fentanyl 1 µg/kg and thiopentone sodium 2.5% sufficient to abolish eyelash reflexes. At 12th minute of starting infusion vecuronium bromide 0.1mg/kg was given to facilitate laryngoscopy and endotracheal intubation. The lungs were ventilated by mask for 3 minutes using 100% oxygen. Just at the 15th minute, when infusion was over, Laryngoscopy was performed with a Macintosh laryngoscope and trachea was intubated with appropriate size endotracheal tube.

All intubations were performed by either of the two senior consultants of the department who were blinded for the group and were not a part of the project. Anaesthesia was maintained with isoflurane upto 1% in air with 40% oxygen. After the conclusion of surgery, reversal of muscle relaxation and extubation of trachea was done as per standard. Any untoward effects related to the drug and anaesthesia were noted and attended to appropriately. A fall in MAP by more than 30% from the baseline was treated with Inj mephentermine 3mg IV boluses. A fall in the HR to less than 50 beats/min was treated with Inj Atropine in small aliquots of 0.3mg IV. Patients were followed up post-operatively at hourly basis till 6 hrs from drug administration. Any untoward effects were observed for and noted.

Monitoring: Monitoring was done with Drager multipara monitor (Drager infinity Kappa, Germany). Heart rate was monitored from continuous Electrocardiogram (ECG) source. Non-invasive blood pressure monitoring was done to collect blood pressure data.

Outcome indicators were defined on the basis of following parameters: Heart rate/minute, Systolic arterial pressure (SAP) mm Hg, Diastolic blood pressure (DAP) mm Hg, Mean arterial pressure (MAP) mm Hg, Rate pressure product (RPP). Baseline values (T1) of these parameters were recorded after arrival in OT before administration of any medication. The same parameters were recorded before induction (T2), during intubation i.e. 0 minute after intubation (I 1) and 1 (I 1), 2 (I 2), 3 (I 3), 4 (I 4) & 5 (I 5) minutes after intubation. Rate pressure product was calculated by multiplying heart rate to systolic arterial pressure.

Cleaned and checked data was entered in computer through SPSS version 20.0 to create a database of the study and it was analyzed using same software to assess the outcome of the study. Demographic pattern were analyzed using independent t-test for age and weight and by chi-square test for sex and ASA grades. For analysis of intra group data two sample t-test was applied and for comparison of inter group variation independent t test was applied.

Results

Out of 100 participants 7 patients, 4 of Group C and 3 of Group D, were excluded as intubation was performed after some delay of completion of infusion. In one patient of group D, hypotension was encountered after induction and mephentermine i.v. was given before intubation so was excluded from the study. One patient in group D had Bradycardia and was given 0.3 mg of atropine i.v. and this case was also excluded from analysis. After exclusion of 9 patients, total data of 91 patients, 46 from group C and 45 from group D were analysed. The demographic pattern was comparable between the groups (Table 1).

Heart Rate response: There was statistically significant rise in the mean heart rate in Group C,
during EI from 82.82 ± 13.37 to 115.86 ± 13.12 (p<0.001). The mean heart rate till 5th minutes after intubation was higher than the basal value (Graph 1). And the differences at all time intervals after intubation was very highly significant (p<0.001). In Group D, there was a decrease in mean heart rate at preinduction from basal value of 86.74 ± 15.37 to 76.00 ± 14.77 (p<0.001). The mean heart rate during EI (I) and also at one minute after intubation came to near basal level 87.82 ± 15.41 (p>0.05).

**Systolic blood pressure (SAP) response:** In Group C, the mean systolic arterial pressure increased to a very high level (17.56%) above basal value from 125.60 ± 8.55 to 147.66 ± 8.38 at laryngoscopy and intubation (p<0.001). And remained high up to 5th minute after intubation. In Group D, the mean systolic arterial pressure decreased at preinduction (T2) from basal value of 127.56 ± 8.11(T1) to 120.72 ± 8.20 (p<0.01). At the time of laryngoscopy and intubation (I), the mean systolic arterial pressure rose (7.90% above basal value) to 137.64 ± 7.18 (p<0.001). There after SAP was lower than baseline at all intervals of time. When both the groups were compared for control of mean systolic arterial pressure (Table 7) it was found that SAP increased in both groups during and after laryngoscopy and intubation. But the increase in control group (17.56% above base line) was much more than dexmedetomidine group (7.90% above baseline).

**Diastolic arterial pressure (DAP) response:** In both the groups, diastolic arterial pressure increased to statistically significant level at EI.

**Mean arterial pressure (MAP):** In Group C, the mean arterial pressure showed an increase from baseline value of 94.43 ± 7.13 to 110.49 ± 6.47 after intubation (p<0.001). And remained significantly higher (p<0.001) till 5th minute.In Group D, the mean arterial pressure showed a fall from 96.21 ± 5.86 to 92.20 ± 7.92 at preinduction. This fall had no statistical significance (p>0.05). At laryngoscopy and intubation, it rose (5.77% above basal value) to 101.76 ± 5.26(p<0.001). On comparison of both groups, it was found that the difference between the two was very highly significant statistically (p<0.001) at all intervals of time, at and after intubation.

**Rate Pressure Product (RPP) response:** In the present study, the basal RPP in Group C, was 10382.88 ± 1698.05. The RPP at laryngoscopy rose (64.5% above basal value) to a high value i.e. 17084.28 ± 1923.18(p<0.001). Post intubation till 5th minute, the RPP was higher than the basal value. In Group D, basal RPP was 11062.62 ± 2078.82. It showed a fall at preinduction to 9175.50 ± 1893.94 (p<0.001). It rose to 12084.18 ± 2083.18 at laryngoscopy and intubation. This rise (10.9% above basal value) was just significant statistically (p<0.05). Then again RPP started falling. At 1 minute after intubation it came to near basal value and the difference was statistically not significant (p>0.05). Thereafter the value of RPP was lower than the basal value at all intervals of time which was statistically very highly significant (p<0.001).

### Table 1: Demographic Pattern

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group C</th>
<th>Group D</th>
<th>Statistical results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>36.45± 6.72</td>
<td>39.55± 7.85</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Weight (in Kgs)</td>
<td>56.68 ± 12.45</td>
<td>49.86 ± 9.21</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>28/18</td>
<td>31/12</td>
<td>X²=0.88 , p&gt;0.05</td>
</tr>
<tr>
<td>ASA grade (I/II)</td>
<td>36/10</td>
<td>34/9</td>
<td>X² =0.54, p&gt;0.05</td>
</tr>
</tbody>
</table>

*Chat 1: Flow chart of patient recruitment*

136 patients were screened for participation in the study

100 patients were enrolled and divided into two groups of 50 each

Group C n=50

Group D n=50

- 4 patients were excluded due to delayed intubation
- 3 patients were excluded due to delayed intubation, 1 due to hypotension and 1 due to Bradycardia excluded.
Dexmedetomidine as an adjunct to anaesthetic induction to attenuate...

Fig. 1: Heart rate response variability between groups

Graph 2: Systolic blood pressure variability between groups

Fig. 3: Diastolic blood pressure variability between groups

**Mean heart rate at different time intervals**

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**Mean SAP at different time intervals**

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**Mean DAP at different time intervals**

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Discussion

We conducted this prospective study in an attempt to assess the efficacy of infusion of dexmedetomidine for haemodynamic stability during peri-intubation period. Laryngoscopy and endotracheal intubation acts as mechanical stimuli to activate sympathoadrenal system and cause significant haemodynamic perturbations like tachycardia, hypertension and fatal arrhythmias sometimes.

The haemodynamic response is a reflex phenomenon. This is mediated by vagus (X) and glossopharyngeal (IX) cranial nerves. Vagus and glossopharyngeal nerves carry the afferent stimuli from epiglottis and infraglottic region and activate vasomotor centre to cause a peripheral sympathetic adrenal response to release adrenaline and noradrenaline. (8)

The hemodynamic response, being transient in nature, may not be of much clinical significance in normal individuals. However, in patients with limited myocardial reserve, the tachycardia and hypertension may result in myocardial ischemia, infarction (MI), arrhythmias or precipitate cardiac failure. (1) The hypertensive response may produce deleterious effects in patients with raised intracranial pressures (ICP) or intraocular pressures (IOP), pheochromocytomas and vascular lesions such as intracranial arterio-venous malformations or those with aortic aneurysms and dissection. (1,9)

Various nonpharmacological and pharmacological methods have been tried to attenuate these cardiovascular reflexes. The non pharmacological method includes but not limited to smooth and gentle intubation with a shorter duration of laryngoscopy. Pharmacological agents like Intravenous Fentanyl (10), buprenorphine (11), lignocaine (12), esmolol (13), Propranolol (14), nifedipine (15), magnesium sulphate (16), alpha-2 adrenergic agonist e.g. clonidine (17,18) and others have been tried to attenuate these cardiovascular responses. Although dexmedetomidine administration has many other perioperative advantages but this study was focussed only to attenuation of cardiovascular responses during peri-intubation period.

The α2-adrenergic agonists provide sedation, anxiolysis, hypnotis, analgesia, and sympatholysis. Dexmedetomidine is a more selective α2 agonist with a 1600 greater selectivity for the α2 receptor compared with the α1 receptor. The basic effects of Dexmedetomidine on the CVS are a decrease in HR &
SVR with an indirect decrease in myocardial contractility, CO & systemic BP. Infusion of dexmedetomidine in volunteers also has been shown to result in a compensated reduction in systemic sympathetic tone without changes in baroreflex sensitivity.

In study done by Keniya et al (18) all patients were premedicated with injection glycopyrolate 0.2 mg. But glycopyrolate is not routinely used as a premedicant before general anaesthesia. As we know that glycopyrolate do increase heart rate, premedication with the same must have interfered with the usual heart rate responses to intubation. So we didn’t premedicate our patients with glycopyrolate.

The results of our study concurred with the study of Pokheran et al (20) study of Laha et al. (21) Although it was even better attenuation of haemodynamic responses in their studies that can be explained by higher doses of dexmedetomidine 1 µg/kg body weight was used.

The results of our study were very similar to study done by Scheinin et al. They reported that 0.6 µg/kg dexmedetomidine decreased, but not totally suppressed, the hemodynamic response to tracheal intubation in healthy individuals. (22)

Anish et al compared dexmedetomidine and clonidine for attenuation of haemodynamic responses to endotracheal intubation and found that dexmedetomidine attenuates these obnoxious responses more effectively. (23)

Reddy et al compared dexmedetomidine and esmolol for this purpose and found that dexmedetomidine attenuates these haemodynamic reflexes as effectively as esmolol. (24)

Dexmedetomidine was well tolerated, and no serious side effects or adverse reactions occurred in the present study.

The cardiovascular responses to laryngoscopy and endotracheal intubation are potentially harmful and methods to obviate these responses have been particularly useful in vulnerable and critically ill patients. For the attenuation of pressure responses to laryngoscopy and endotracheal intubation, an agent with quick onset and short duration, without any deleterious effect or minimum drug interaction with high therapeutic index should be considered as an ideal agent. An ideal agent is still not available and the search should continue for an ideal agent. Single shot intravenous dexmedetomidine is simple, effective and acceptable mean to attenuate the pressure response to laryngoscopy and endotracheal intubation. However, the study has to be continued in more number of patients and also in patients with hypertension and ischemic heart disease for further evaluation.

In our study it was observed that dexmedetomidine effectively attenuated the tachycardic response to intubation.

Conclusion
From the present study, it is concluded that pretreatment with dexmedetomidine 0.5µg/kg attenuated the sympathoadrenal response to laryngoscopy and endotracheal intubation effectively, but could not obtund it completely. It was also inferred that tachycardiac response was better attenuated than pressure response.

References