Clinical evaluation of dexmedetomidine on haemodynamic stress response during laryngoscopy and intubation: A randomized double blind parallel group placebo controlled study

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Abstract
The physiological changes caused by laryngoscopy and intubation are due to sympathetic discharge leads to increase in blood pressure, heart rate, oxygen consumption, leading to haemodynamic instability which may cause myocardial ischemia, left ventricular failure or cerebral hemorrhage.

Aims And Objective: To assess the efficacy and safety of dexmedetomendine in attenuating haemodynamic stress response to laryngoscopy and endotracheal intubation.

Materials and Methods: After institutional review board approval, 100 patients posted for planned surgery were randomized in to two groups to receive 100 ml of normal saline in Group C and Inj. dexmedetomidine 1µg/kg in 100 ml of normal saline in Group D intravenously over 10 minutes, 30 minutes before induction. Standard general anaesthesia was given to all patients. Patients were monitored for haemodynamic changes and Sedation score at various specific timings as per the protocol.

Result: There was significant decrease in heart rate and blood pressure after giving infusion of dexmedetomendine and remain stable during and after laryngoscopy and intubation.

Conclusion: We conclude that dexmedetomendine in a dose of 1µg/kg given half an hour before induction effectively blunts the haemodynamic response to laryngoscopy and endotracheal intubation.

Keywords: Hemodynamic stress response, Laryngoscopy, General anaesthesia, Dexmeditomidine.

Introduction
In the era of modern anaesthesia and surgery, the key factor is safe outcome. Anaesthetic drugs, complicated surgical procedures and patient’s condition due to co-existing medical diseases increase the risk. With the use of newer safe drugs, continuous monitoring and management of perioperative events with excellent care in the post operative units have reduced the morbidity and mortality for last few decades.

The series of physiological changes (the pressure response to laryngoscopy and tracheal intubation) leads to an endocrine response as adrenaline and noradrenaline secretion by the stimulation of sympathetic nervous system.1,2 The elevated catecholamine concentration in plasma due to sympathetic discharge increases the arterial blood pressure, heart rate and oxygen consumption, leading to haemodynamic instability.3,4

The rise in blood pressure and heart rate usually occurs about 15 seconds after laryngoscopy and becomes maximal after 30-45 seconds. Thus, limiting laryngoscopy to 15 seconds or less can minimize blood pressure elevation. Usually these changes are transient and well tolerated by healthy individuals, but may be fatal in patients with hypertension, coronary artery diseases and cerebrovascular diseases.4 This pressure response may predispose to development of pulmonary edema, acute LVF, dysrrhythmias, intraoperative MI and CVA.5-10

To attenuate sympathetic discharge and provide hemodynamic stability various agents such as volatile anaesthetics,11 topical and IV lidocaine,12-14 opioids,15-17 vasodilators like Sodium nitroprusside,18 Nitroglycerine,19 Calcium channel blockers,20,21 Beta blockers22-25 and alpha 2 agonist26 have been used in general anaesthesia.

Among these alpha 2 agonist such as clonidine and dexmedetomidine have actions on α2 adrenoceptors, but dexmedetomidine is highly specific and selective α2 agonist with α2: α1 binding selectivity ratio of 1620 : 1 compared to 220: 1 for clonidine.27

It has become evident by various studies28-35 that, α2 adrenoceptor agonists may be a useful class of drugs in conjunction with anesthesia. Dexmedetomidine has property of good anxiolysis, sedation and analgesic action. It also decreases the dose and MAC value of inhalational anaesthetic agents36,37 and prevents postoperative nausea, vomiting and shivering and allows psychomotoric function to be preserved while letting the patient rest comfortably.

The present study was aimed at attenuation of haemodynamic stress response to laryngoscopy and intubation in patients posted for elective surgeries under GA requiring endotracheal intubation, with single IV dose of Inj. Dexmedetomidine 1microgram/kg given 30 minutes before induction.

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Materials and Methods

After approval from the institutional review board and informed written consent from patient, this randomized prospective double blind study carried out in 100 patients aged 20-60 years of ASA physical status of I and II scheduled for elective surgery under general anaesthesia requiring endotracheal intubation.

After detailed preanaesthetic evaluation, systemic examination and routine investigations, patient with major systemic disease like COPD, renal disease, cardiac diseases, diabetes, patients on antipsychotic drugs, pregnant patient and anticipated difficult intubation were excluded from this study.

In pre-anesthetic preparation room, monitoring for heart rate, non-invasive blood pressure (systolic, diastolic and mean arterial pressure), and peripheral oxygen saturation were established and baseline vital parameters were recorded, including Ramsay sedation score. Intravenous line was secured and premedication consisting of Ondansetron 0.08 mg/kg IV and Glycopyrrolate 0.004 mg/kg IM, were given 30 minutes before induction of anesthesia.

Patients were randomly divided into two groups (each of 50 patients) using random number table method.

**Group D**, (n=50): Inj. dexmedetomidine 1 mcg/kg in 100 ml NS

**Group C**, (n=50): 100 ml NS

Intravenous infusion over 10-15 minutes, 30 minutes before induction of anesthesia.

Patients were monitored for hemodynamic changes at various specific timing as per protocol, and sedation was monitored according to Ramsay Sedation Score (as mentioned below) immediately and at 5, 10, 15 and 20 minutes after drug administration.

**Ramsay Sedation score:**

<table>
<thead>
<tr>
<th>Score</th>
<th>Level of sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Awake and agitated.</td>
</tr>
<tr>
<td>1</td>
<td>Awake and comfortable.</td>
</tr>
<tr>
<td>2</td>
<td>Asleep but arousable.</td>
</tr>
<tr>
<td>3</td>
<td>Asleep with sluggish response to verbal command and touch.</td>
</tr>
<tr>
<td>4</td>
<td>Asleep with no response to verbal command and touch.</td>
</tr>
</tbody>
</table>

In the operation theatre multipara monitor was attached and vital parameters were recorded.

1. In the operation theatre multipara monitor was attached and vital parameters were recorded.
2. Standard general anaesthesia was given to all patients.
3. All the parameter were recorded at various specific timings as per protocol.
4. Hypotension was defined as a decrease in systolic blood pressure > 30% of the baseline value or systolic blood pressure < 100 mm Hg, and treated with intravenous blouses of 6 mg ephedrine and crystalloid fluids.
5. Hypertension was defined as increase in blood pressure > 30% of the baseline value and treated with Inj. NTG i.v. Infusion
6. Bradycardia was defined as a pulse rate of < 60 beat/min and will be treated with bolus of 0.6 mg atropine.
7. Tachycardia was defined as pulse rate of > 100 beats/min and was treated with beta blockers
8. Any treatment required and complication if any, was recorded till 30 min after intubation.
9. At the end of surgery, neuromuscular blockade was reversed with neostigmine 50 microgram/kg and glycopyrrolate 10 microgram/kg IV.
10. After satisfying the extubation criteria, trachea was extubated and patients were transferred to post anaesthesia care unit.

**Statistical Analysis**

The data obtained in the study for various parameters were presented in the tabulated form. Using statistical software (graph pad prism statistical software) mean and standard deviation were calculated for all the quantitative variables. Intra group comparison was made using paired student t-test and comparison among different groups (inter group comparison) was done using unpaired t-test. P value <0.05 was considered statistically significant.

**Observation and Results**

<table>
<thead>
<tr>
<th>Demographic profile</th>
<th>Group C</th>
<th>Group D</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>33.48±8.21</td>
<td>34.66±8.82</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>29/21</td>
<td>31/19</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Weight (kg) (Mean ± SD)</td>
<td>56.76±7.60</td>
<td>55.42±7.72</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>ASAPS (I-II)</td>
<td>40/10</td>
<td>42/8</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Patient characteristics in terms of age, gender and weight were comparable in both the groups.
On comparing the changes in heart rate between group C and group D at various specific timing, there was significant difference between the two groups (p<0.05).

On comparing the changes in SBP between group C and group D at various specific timings, there was statistically significant difference between the two groups (p<0.05).
Fig. 3: Changes in diastolic blood pressure in two groups

On comparing the changes in DBP between group C and group D at various specific timings, there was statistically significant difference between the two groups (p<0.001).

Fig. 4: Changes in mean arterial pressure in two groups

On comparing the changes in MAP between group C and group D at various specific timings, there was statistically significant difference between the two groups (p<0.001).

Fig. 5: Changes in SpO2 in two groups
Spo2 remained stable and comparable in both the groups throughout the study period (p>0.05).

Fig. 6: Sedation score in two groups

The difference in sedation score was significant between group C and group D after drug administration (p<0.001). Sedation did not cause respiratory depression in any patient.

Table 2: Complications (Adverse Events)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Group C</th>
<th></th>
<th>Group D</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>18</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

In group C, 18 patients (36%) had tachycardia, 16 patients (32%) had hypertension and 3 patients (6%) had arrhythmia intraoperative.
In group D, 5 patients (10%) had bradycardia and 2 patients (4%) had hypotension, preoperative. Intraoperative, 3 patients (6%) had tachycardia and 2 patients (4%) had hypertension.
Respiratory depression was not seen in any patient of either group.

Table 3: Patients needed treatment for complications in two groups

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Group C</th>
<th></th>
<th>Group D</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of pts</td>
<td>%</td>
<td>Number of pts</td>
<td>%</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>12</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inj. Atropine</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Inj. NTG Infusion</td>
<td>13</td>
<td>26</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

In group C, 13 patients (26%) needed Inj. NTG infusion in titrated dose to achieve baseline MAP value, intraoperative.
In group D, 5 patients (10%) needed Inj. Atropine (0.6 mg) IV to overcome bradycardia after drug administration, preoperative. Intraoperative, 1 patient (2%) needed Inj. NTG infusion.

Discussion
Stress response under anaesthesia has been universally recognized phenomenon. Stress response is accompanied by an increased nervous system activity in sympathetic efferent tracts resulting in adrenergic response. This adrenergic response (increase in catecholamine level) may be associated with severe hypertension, tachycardia which in turn may cause cardiac arrhythmias, myocardial ischemia and left ventricular dysfunction.3,4

Direct laryngoscopy and endotracheal intubation are noxious stimuli that can provoke stress response in the cardiovascular, respiratory and other physiological systems. The magnitude of response is greater with increasing force and duration of laryngoscopy. To blunt this pressure response, various pharmacological agents such as lignocaine, fentanyl, beta blockers and alpha 2 agonist have been studied till date.

Alpha 2 adrenergic agonist has beneficial effect on hemodynamic response to endotracheal intubation. It
attenuates stress-induced sympathoadrenal response to painful stimuli, improves the intraoperative hemodynamic stability and reduces the incidence of perioperative myocardial ischemia. It has wide varieties of actions like anxiolytic, sedation, analgesia, prevention and treatment option. Dexmedetomidine is a newer highly selective α2-agonist that has been shown to have sedative, analgesic, sympathetic and anaesthetic sparing effects.\textsuperscript{19,26} It causes dose dependant decrease in arterial blood pressure and heart rate, associated with decrease in serum norepinephrine concentration.\textsuperscript{35} Its α2:α1 binding selectivity ratio is 1620:1 compared to 220:1 for clonidine.\textsuperscript{38} Hence, dexmedetomidine may be a better drug among α2-agonists for suppressing the haemodynamic responses to laryngoscopy and intubation.

Dexmedetomidine has been found effective in blunting the stress response to laryngoscopy and intubation by few authors,\textsuperscript{24-31} hence to contribute to the literature, we decided to study the efficacy and safety of dexmedetomidine in attenuating haemodynamic stress response during laryngoscopy and intubation and to assess its sedative effect in a dose of 1 μg /kg administered over 10 minutes, 30 minutes before induction.

Kallio et al\textsuperscript{31} showed that the maximum inhibition of sympathetic nervous system activity occurred at 50 and 75 μg doses of dexmedetomidine.

Aho M, et al\textsuperscript{34} studied the effect of two doses of dexmedetomidine (0.3 μg/kg & 0.6μg/kg) and fentanyl (2μg/kg) on haemodynamic response to laryngoscopy and intubation in women undergoing abdominal hysterectomy. They concluded that dexmedetomidine at a dose of 0.6μg/kg administered before induction blunted the tachycardiac response during endotracheal intubation and the post intubation increase in heart rate was significantly less compared to the fentanyl group.

M.L. Jaakola, et al\textsuperscript{35} studied the effect of a single intravenous bolus dose of dexmedetomidine (0.6 μg/kg) on intraocular pressure, hemodynamic & sympathoadrenal responses to laryngoscopy & tracheal intubation. They observed that in dexmedetomidine group, there was 34% reduction in intraocular pressure & 62% reduction in plasma nor-adrenaline concentrations. After intubation, maximum heart rate was 18% less in dexmedetomidine group compared with placebo. They also noted that there was decrease in blood pressure in dexmedetomidine group.

Similar to above studies, in our study there was significant fall in heart rate in dexmedetomidine group after drug administration (p<0.05) as compared to baseline. There was increase in heart rate at the time of laryngoscopy and intubation but this increase was not significant (p>0.05). After intubation, heart rate returned below baseline value (p<0.05) and remained stable throughout the study period. While in control group, heart rate significantly increased during laryngoscopy and intubation and remained above baseline (p<0.05) throughout the study period. We also observed mild increase in SBP, DBP and MAP during laryngoscopy and intubation in dexmedetomidine group, which was not significant (p>0.05). Thereafter, blood pressure decreased and remained so throughout the study period. While in control group, there was significant rise in MAP during laryngoscopy and intubation and this increase was remained so throughout the study period. Similar results were found by Hall et al,\textsuperscript{37} that biphasic cardiovascular changes, where blood pressure decreased followed by a momentary rise in blood pressure after an injection of dexmedetomidine, occurred after infusion of dexmedetomidine in dose of 0.2-0.6 μg/kg. They reported that an insignificant rise in blood pressure had continuously been exhibited for 10 min after an initial injection of dexmedetomidine, and the heart rate decreased significantly. MAP decreased after drug infusion below baseline value (p<0.05) without fluctuation in dexmedetomidine group. Changes in blood pressure during laryngoscopy and intubation was comparable to baseline value.

Tachycardia was treated with beta blockers (Inj. Metoprolol or Inj. Esmolol). Tachycardia with hypertension (MAP rise <20%) was treated by increasing inhalational agent while, MAP rise >20% was treated with Inj. NTG in titrated dose according to response.

In control group, 12 patients needed beta blockers and 4 patients needed Inj. NTG infusion in titrated dose to achieve baseline MAP value, while no patient needed any treatment in dexmedetomidine group. Dexmedetomidine enables a smooth transition from the time of administration of reversal to the post-extubation phase by suppressing the CNS sympathetic activity, leading to a high quality of extubation, as was observed in majority of our patients in
dexmedetomidine group. Moreover, dexmedetomidine reduces requirement of inhalational anaesthetic agent intraoperatively\(^24\)^\(^28\)^\(^29\) which helps in smooth and rapid recovery.

In our study, no delayed recovery was noted in any patient receiving dexmedetomidine. Sedation score was maximum of 1 without respiratory depression.

**Conclusion**

Dexmedetomidine in a dose of 1 mcg/kg given half an hour before induction effectively blunts the hemodynamic response to laryngoscopy and endotracheal intubation and provides stable hemodynamic through the surgery and provides good and safe level of sedation without respiratory depression in routine surgery.

**Conflict of Interest:** None.

**References**


