EFFECT OF DEXMEDETOMIDINE ON HEMODYNAMIC PARAMETERS DURING EXTUBATION. A PROSPECTIVE RANDOMIZED DOUBLE BLIND STUDY

SHRUTHI AH*, NETHRA SS**, SUDHEESH K***, DEVIKA RANI D****
AND RAGHAVENDRA RAO RS*****

Background: Extubation is known to produce significant hemodynamic disturbances. There is a need to avoid increase in heart rate and blood pressure in hypertensive and cardiac patients and in vascular, neuro and intraocular surgeries.

Aims: To study the ability of dexmedetomidine to attenuate the hemodynamic responses during extubation.

Materials and methods: 80 patients of ASA Grade I-II aged 18-50 years received standard anesthesia. At the closure of skin incision, patients were randomly allocated to receive either dexmedetomidine 0.5 µg/kg (Group D) or saline placebo (Group C) intravenously over 10 minutes in a double-blind design. Heart rate (HR), systolic, diastolic and mean arterial pressures (SBP, DBP, MAP) were assessed before, during and after extubation. Time to eye opening and extubation, sedation, complications such as coughing, laryngospasm, bronchospasm and desaturation were recorded.

Results: HR, SBP, DBP and MAP were comparable to basal values in group D at extubation and lower than baseline values post-extubation but significant increase was noted in group C (P <0.001). Time to extubation and eye opening were prolonged in Group D (P <0.001). Incidence of hypotension was more in group D (22%) but was transient. Incidence of coughing was lower in Group D than in group C (P <0.001). Patients in group D were more sedated for 30 minutes post extubation.

Conclusion: Dexmedetomidine 0.5 µg/kg given before extubation attenuates hemodynamic reflexes during emergence from anesthesia without causing undue sedation, but prolongs time to extubation.

Keywords: Dexmedetomidine, general anesthesia, extubation, hemodynamic responses.

Introduction

Tracheal intubation and extubation are accompanied by raised sympathoadrenal activity with an increased plasma catecholamine levels which cause an increase in heart rate, myocardial contractility and systemic vascular resistance\(^1\). Majority of patients tolerate these changes without any significant consequences\(^1\) but patients with co-existing diseases like hypertension and diabetes may not be able to tolerate these responses.

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An increase in heart rate is more likely to produce signs of myocardial ischemia due to the increased myocardial oxygen demand than hypertension. A recommendation is to maintain heart rate and blood pressure during intubation and extubation within 20% of normal awake value of that patient.

Various options in vogue to attenuate extubation response include: deeper planes of anesthesia, topical anesthesia, use of intravenous local anesthetics, calcium channel blockers, opioids, and sympathetic blockers etc. Alpha₂-agonists simultaneously potentiate the effects of general anesthetics, reduce their dose requirements, and attenuate sympathoadrenal responses to noxious stimuli encountered during anesthesia and surgery, thus providing improved hemodynamic, metabolic, and hormonal stability. Dexmedetomidine, is a highly selective alpha₂-adrenergic agonist that has sedative, anxiolytic and analgesic actions. It is known to exhibit dose dependent attenuation of the stress response to intubation. However not enough literature is available with regard to its effect on hemodynamic response to extubation. The aim of the current study is to assess the effect of dexmedetomidine when given at a dose of 0.5 µg/kg just before extubation on hemodynamic responses to emergence from anesthesia. Its effect on recovery was the secondary aim of the study.

Materials and Methods

A prospective, randomized, double blind case controlled study was conducted on 80 patients undergoing various elective surgeries under general anesthesia with endotracheal intubation at a tertiary level medical college hospital during the period between September 2010 to 2012. Institutional ethical committee approval was obtained.

Patients aged between 18 to 50 years belonging to American Society of Anesthesiology (ASA) physical status I and II were included in the study. Patient refusal, those with cardiac or pulmonary disease or any endocrinological disorder, head and neck surgeries, those with history of drug abuse or psychological disorder and obese patients, with difficult airway or history of sleep apnoea were excluded from the study.

Preanesthetic evaluation was done on the day prior to the surgery. A detailed history of present and past medical illnesses and history of drug allergies if any was recorded. Patients were advised overnight fasting and premedicated with oral ranitidine 150 mg and oral alprazolam 0.5 mg on the day before surgery.

After obtaining informed written consent, patients were randomly divided into 2 groups based on software generated random number table (www.random.org). The details of randomization and group allocation was with the principal investigator and not revealed to others till the completion of collection of data. The drug or placebo for infusion was prepared by a technician unaware of the study, as per the instructions of the principal investigator. The anesthesiologist who administered the drug or placebo solution and monitored the patient subsequently, and the patient were unaware of the content of the solution.

After shifting patient to the operating room, intravenous access was obtained and ringer lactate solution started. All patients were monitored with electrocardiography (ECG), pulse oximetry, non-invasive blood pressure (NIBP), end tidal carbon-dioxide (Et CO₂), and train of four (TOF) (hemodynamic and neuromuscular monitoring modules of Avance S5™ anesthesia workstation) and basal parameters were recorded.

Glycopyrrolate 5 µg/kg, midazolam 0.025 mg/kg and fentanyl 2 µg/kg were administered intravenously just before induction of anaesthesia. Intravenous propofol 2 mg/kg was used for induction and intubation was facilitated with intravenous atracurium 0.5 mg/kg. Anesthesia was maintained with 66% nitrous oxide in oxygen and isoflurane 1%-2% titrated to maintain adequate depth of anesthesia, based on hemodynamic parameters. Muscle paralysis was maintained with a continuous infusion of atracurium. Atracurium infusion was started at a dose of 10 µg/kg/hr, 15 minutes after the administration of intubating dose, as guided by TOF count and titrated subsequently to maintain TOF count less than 2. Fentanyl 1 µg/kg was administered if there was an increase in heart rate and systolic blood pressures more than 20% baseline, despite of administration of 1.3 MAC of isoflurane.

At the beginning of the closure of skin incision, isoflurane was turned off and atracurium infusion stopped.
Group D (n=40) patients: received 0.5 µg/kg of dexmedetomidine diluted to 10 ml in normal saline. Group C (n=40) patients: received 10 ml of normal saline (placebo) prior to extubation. Both infusions were given over 10 minutes.

Nitrous oxide was stopped following end of infusion.

Residual neuromuscular blockade was reversed using neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg intravenously when TOF count was 4. Patients in both groups were extubated when all the following subjective and objective criteria were fulfilled:

1. Sustained head lift for 5 seconds.
2. Sustained hand grip for 5 seconds.
3.obeys commands.
4. Tidal volume >6 ml/kg.
5. TOF ratio 0.9.

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), percentage saturation of oxygen (SpO2) and respiratory rate (RR) were recorded every 5 minutes intraoperatively; immediately prior to drug or placebo infusion; at 1, 2, 5, 7 and 10 minutes during infusion; following reversal administration; and then post extubation every 5 min for 15 min, and then every 15 min for next 2 hours thereafter.

Bradycardia was defined as HR <60 beats per minute (bpm), tachycardia being 20% increase from baseline, hypertension as either 20% increase from baseline or SBP >180 mm of Hg and hypotension as 20% decrease from baseline or SBP <80 mm of Hg.

Time to extubation and time to eye opening, i.e interval between cut off of nitrous oxide to extubation and eye opening respectively were recorded.

Sedation was evaluated using Ramsay Sedation Scale12. Complications such as coughing, laryngospasm, bronchospasm or desaturation were noted.

With the power of study being 80% and confidence limits at 95%, a minimum sample size required to detect 30% difference in heart rate between study and control groups, was 24 patients in each group. We conducted study with 40 patients in each group to make it more authentic. Descriptive and inferential statistical analysis was carried out. Results on continuous measurements are presented on Mean ± SD (standard deviation) and results on categorical measurements are presented in Number (%). Student test (two tailed, independent) was used to test the significance of study parameters on continuous scale for intergroup and intragroup analysis on metric parameters. Levene’s test for homogeneity of variance was performed to assess the homogeneity of variance. Chi-square/Fisher Exact test was used to test the significance of study parameters on categorical scale between two groups. Statistical software SPSS version 17.0 was used for the data analysis. P value <0.05 was considered statistically significant.

Results

Both the groups were comparable with respect to age, sex, body weight and duration of surgery (Table 1).

<table>
<thead>
<tr>
<th>GROUP C (n=40)</th>
<th>GROUP D (n=40)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(yrs)</td>
<td>33.7 ± 11.1</td>
<td>34.9 ± 10.7</td>
</tr>
<tr>
<td>gender(M/F)</td>
<td>20/20</td>
<td>18/22</td>
</tr>
<tr>
<td>duration of surgery(min)</td>
<td>65.7 ± 21.7</td>
<td>62.9 ± 22.2</td>
</tr>
<tr>
<td>weight(kg)</td>
<td>56.1 ± 9.8</td>
<td>56.8 ± 9.8</td>
</tr>
<tr>
<td>ASA(I/II)</td>
<td>34/6</td>
<td>35/5</td>
</tr>
</tbody>
</table>
Basal heart rate (HR) was comparable in both the groups. In group D, HR was comparable to basal value from 5th minute of the start of drug infusion and at extubation, however it was lower than basal value post extubation till 30 minutes whereas HR in group C showed a steady rise compared to preoperative values which was significant (P < 0.001) at all these time intervals. Intergroup comparison of heart rate at various time intervals showed clinically and statistically significant reduction in group D compared to group C (Figure 1).

Both groups were comparable with respect to basal SBP, DBP and MAP values. SBP and DBP values were comparable to preoperative values in Group D from 7th minute of the start of dexmedetomidine infusion till post extubation for 30 min but the respective values were significantly higher in group C. Comparison of SBP and DBP values at these time intervals showed significant reduction in group D than group C. Beyond 30 minutes SBP and DBP values were comparable between the two groups (Figure 2).

SpO₂ (%) and RR (breaths per minute) in both the groups were comparable at all time intervals (P > 0.05).

The Ramsay sedation scale was significantly higher in patients of Group D compared to patients of Group C at the time of extubation and at 5, 10, 15 and 30 minutes post extubation (Figure 3). However the average Ramsay sedation score was < 3 in patients of Group D and all patients were easily arousable. Time to extubation in group D was 18.70±3.36 minutes compared to 15.24±1.60 minutes in group C (P < 0.001), and time to eye opening was 17.04±3.19 minutes and 13.88±1.55 minutes in group D and C respectively (P < 0.001).

Table 2
Comparison of incidence of complications in the two groups

<table>
<thead>
<tr>
<th>Complications</th>
<th>Group C (n=40)</th>
<th>Group D (n=40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension, n(%)</td>
<td>0(0%)</td>
<td>9(22.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>28(70%)</td>
<td>0(0%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0(0%)</td>
<td>2(5%)</td>
<td>0.562</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>29 (72.5%)</td>
<td>2(5%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Agitation</td>
<td>9(22.5%)</td>
<td>0(0%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Coughing</td>
<td>12(30%)</td>
<td>2(5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Desaturation</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Incidence of hypotension was higher in Group D versus Group C. However, incidence of hypertension, tachycardia, agitation, and coughing were higher in Group C versus Group D (Table 2). Incidence of laryngospasm, bronchospasm, and oxygen desaturation were not different between the two groups.

Discussion

The present study shows that administration of
0.5 µg/kg of dexmedetomidine as an infusion over 10 minutes at the time of skin closure will attenuate hemodynamic responses to extubation and provides smooth extubation.

Complications at extubation include hypertension, tachycardia, dysrhythmias, myocardial ischemia; coughing; laryngospasm and bronchospasm; impaired laryngeal competence and pulmonary aspiration and hypoventilation\(^{13,14}\). Untreated tachycardia or hypertension from the increased sympathoadrenal activity will result in increased myocardial oxygen consumption, resulting in myocardial ischemia in patients at risk (patients with diabetes mellitus, cardiac disease, pre-eclampsia and those undergoing intracranial, intraocular or vascular surgeries)\(^ {3,8,15,16}\). Coughing at the time of extubation is mainly attributed to the presence of secretions in oral cavity and tracheobronchial tree\(^ {17}\) and by itself can result in tachycardia, hypertension, myocardial ischemia, increased intracranial and intraocular pressures, bronchospasm and surgical bleeding and wound disruption\(^ {18}\). So the technique or drug chosen at extubation should attenuate hemodynamic disturbance and provide smooth extubation with minimal or no side effects.

Extubation of trachea with patients in a deeper plane of anesthesia avoids cardiovascular stimulation. This can be achieved by inhalation or intravenous anaesthetic agents, opioids or both, however it carries the higher risk of hypoventilation and upper airway obstruction\(^ {13}\). Coughing may be particularly troublesome during “light anesthesia” extubation and
cannot be entirely prevented\textsuperscript{14}.

Dexmedetomidine by its alpha\textsubscript{2} agonist action at multiple sites not only results in decrease in heart rate and blood pressure, by central sympatholysis but also in analgesia, sedation, and anxiolysis\textsuperscript{19}.

Dexmedetomidine has been found to be superior to fentanyl and lignocaine in blunting hemodynamic changes to extubation\textsuperscript{20,21}. In the current study, the heart rate and blood pressures remained below baseline in the post-extubation period and the incidence of tachycardia and hypertension were lower following administration of dexmedetomidine which is concurrent with the observation of earlier studies\textsuperscript{20-22}.

Incidence of bradycardia is higher when a higher dose of dexmedetomidine is used\textsuperscript{22}. Low incidence of bradycardia in the present study may be attributable to the lower dose of dexmedetomidine used. However incidence of hypotension was slightly higher compared to other studies\textsuperscript{23}. Bradycardia and hypotension were both transient and responded to atropine and intravenous fluids respectively in the present study.

Incidence of coughing was significantly lower in the group receiving dexmedetomidine which is in accordance with observations of Aksu R and colleagues\textsuperscript{20}. Guler G and colleagues also noted the effect of dexmedetomidine on children undergoing adenotonsillectomy wherein dexmedetomidine group had significantly decreased incidence and severity of agitation and a smooth extubation without any increase in incidence of side effects when dexmedetomidine was administered intraoperatively\textsuperscript{23}. Alpha\textsubscript{2} agonist activity of dexmedetomidine is known to reduce secretions of mucus glands, glands of oral and tracheobronchial tree in particular\textsuperscript{24}. Reduction in secretions may result in decreased incidence of coughing and other complications such as laryngospasm and bronchospasm. However none of the patients in the present study complained of dry mouth.

Fourty eight percent of patients receiving dexmedetomidine were drowsy (RSS=30) but responded to oral commands following extubation and is in concurrence with the observations of Kothari D et al\textsuperscript{21}. However after 30 min of extubation sedation scores were comparable in both groups. In a study by Bindu B et al, 84\% of patients receiving dexmedetomidine had a sedation score (RSS) of 3 after extubation which was higher compared to the present study and is attributed to use of higher dose of dexmedetomidine\textsuperscript{22}.

Time to extubation and eye opening were significantly prolonged in the dexmedetomidine group. This observation is in agreement with study conducted by by Guler G and colleagues on emergence agitation wherein time to extubation and emergence were prolonged significantly\textsuperscript{23}. However Erdil F and colleagues observed a contradictory finding in pediatric patients receiving sevoflurane, where time to extubation and eye opening were similar to that of control group\textsuperscript{25}.

The major limitation of this study is that it is rather focused on general population and quality of extubation was not studied. Future studies may be done in specific patient populations such as geriatric, neurosurgical and ophthalmic patients where extubation responses are equally critical to that of intubation responses.

**Conclusion**

The present study demonstrates that dexmedetomidine 0.5 µg/kg given before extubation attenuates the airway and hemodynamic reflexes during emergence from anesthesia while providing smooth extubation without causing undue sedation.
References


Append

Ramsay Sedation Scale12.
1- Anxious and agitated, restless.
2- Co-operative, oriented, tranquil.
3- Responsive to verbal commands, drowsy.
4- “Asleep”, responsive to light stimulation.
5- Asleep, slow response to stimulation.
6- No response to stimulation.
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**REFERENCES**
1. BRIDION Summary of Product Characteristics (SPC).

Please see summary of product characteristics for full prescribing information.

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