Original Article

Efficacy of dexmedetomidine in attenuating hemodynamic and airway responses during extubation: a randomized double-blind study

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Abstract

Background
Tracheal extubation causes significant hemodynamic changes and airway irritation. During smooth extubation there is absence of straining, movement, coughing, breath holding, laryngospasm and minimal change in hemodynamic. Purpose of this study was to evaluate the efficacy of dexmedetomidine in attenuating hemodynamic and airway responses during extubation.

Methodology
Eighty patients receiving general anesthesia were included in this randomized double-blind study. Ten minutes before the end of anesthesia, Group D (Dexmedetomidine group) (n=40) received Inj. Dexmedetomidine 0.5mcg/kg and Group N (Normal Saline group) (n=40) received 10 ml normal saline over 10 mins. Heart rate and mean arterial pressure were recorded prior to the drug administration till 10 mins after extubation. The incidence of cough was monitored during extubation. Any possible side effects of study drugs were recorded.

Results
Age, gender, physical status, weight, duration of surgery, baseline heart rate and mean arterial pressure were comparable between the groups. There was statistically significant difference (p < 0.05) in heart rate and mean arterial pressure between the groups after 5 mins of study drug administration and then throughout the study period. Using four point scale for coughing during extubation, 10% of Group D and 50% of Group N had minimal cough, 22.5% of Group N and 2.5% of Group D had moderate cough.

Conclusion
Finding suggests that intravenous dexmedetomidine before extubation significantly attenuates hemodynamic and airway responses during extubation.

Key words: Dexmedetomidine; extubation; general anesthesia; stress response

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Introduction
Tracheal extubation is the discontinuation of an artificial airway when the indications for its placement like general anaesthesia, airway obstruction, protection of airway, suctioning, ventilatory failure and hypoxemia no longer exist. Many
investigators have documented that tracheal extubation causes transient increase in blood pressure and heart rate.\textsuperscript{1,3} Stimulus causing such increase in hemodynamic are multifactorial like, light plane of anaesthesia, pain at surgical site, emergence from anaesthesia or tracheobronchial irritation and reflex sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation.\textsuperscript{4,5} This results in hypertension, tachycardia and arrhythmias, which are usually variable and unpredictable. Airway irritation during tracheal extubation may cause cough or difficulty in breathing which contributes change in hemodynamics.\textsuperscript{5–7} The majority of patients are able to tolerate those responses without any significant consequences. However some patients with co-existing disease may not tolerate these responses.\textsuperscript{8} There is a risk of myocardial ischemia/ infarction, cerebrovascular accident.

Laryngoscopy and tracheal intubation in patient with hypertension, produces greater increase in arterial pressure than in normotensive patients. Thus it is reasonable to expect that hypertensive patients may exhibit an exaggerated hypertensive response to awakening and extubation compared to normotensive patients. Such hypertensive episodes may result in cardiac or cerebral complications.\textsuperscript{9} In the patient with coronary artery disease, hemodynamic response like tachycardia to extubation may lead to imbalance between myocardial oxygen supply and demand, resulting in myocardial ischemia. The occurrence of perioperative myocardial ischemia may be associated with subsequent development of postoperative myocardial infarction.

Sudden increase in arterial pressure may lead to increase in both cerebral blood flow and intracranial pressure. Coughing associated with endotracheal suctioning causes increase in ICP by increasing intrathoracic pressure, cerebral venous pressure and cerebral blood volume. Similarly, rise in intraocular pressure may be hazardous in patients with ophthalmic surgery.\textsuperscript{10} Similarly, such stress may induce postoperative hemorrhage and potentially fatal cervical hematoma after thyroid surgery.\textsuperscript{2} Therefore it is important to prevent or suppress the hemodynamic response to extubation in such patient.  

Smooth extubation requires the absence of straining, movement, coughing, breath holding or laryngospasm and minimal change in blood pressure and heart rate.\textsuperscript{4,5,11,12} Thus, the attempts have been made to oppose the stress response by the use of drugs such as narcotic analgesics, local anaesthetics, adrenoreceptor blockers, vasodilator agents or extubation in deep level of anaesthesia but none of them are completely successful. Dexmedetomidine is highly selective and potent alpha-2 adrenoceptor agonist (alpha-2 to alpha-1 receptor:1620:1), with an unique property of providing sedation and analgesia without respiratory depression.\textsuperscript{13} It has a sympatholytic effect due to decrease in norepinephrine concentration which decreases the heart rate, blood pressure. The presynaptic site of action of alpha-2 receptor modulates the release of norepinephrine and adenosine triphosphate through negative feed-back mechanism. Therefore, dexmedetomidine is theoretically appropriate in reducing airway reflexes and hemodynamic reflexes during tracheal extubation.\textsuperscript{5} Purpose of this study was to evaluate the efficacy of dexmedetomidine in attenuating hemodynamic and airway responses during extubation as well as to record any possible adverse effects.

**Methods**

This was a prospective, randomized, double-blind study conducted at Bir Hospital, Mahaboudha, Kathmandu. The sample size calculation was based on the study done by Ravi Shankar Goarya.\textsuperscript{4} Pooled standard deviation was taken from the mean of heart rate during extubation from the study and power analysis at 5% level of significance and 80%power of study; the sample size was 40 in each group.

The ASA I and II of both gender from 16 to 60 years age posted for elective surgery requiring general anesthesia and endotracheal intubation (except head and neck surgery) and surgery duration of 60-120 mins were included in this study. Patient’s refusal, patient with known allergy to dexmedetomidine; patient with h/o hypertension, ischemic heart disease, aortic stenosis, left ventricular failure, atrio-ventricular conduction block, sinus bradycardia, asthma, chronic obstructive pulmonary disease; patient receiving anti-hypertensive drugs, MAO Inhibitors; pregnant woman; mentally retarded, deaf or dumb patient, anticipated difficult airway, case encountered with difficult intubation were excluded from the study.
The study was conducted after approval from the Institutional Review Board. Preanesthetic check up was done a day before surgery. Informed written consent was obtained from the patient before enrollment in the study. Patients were kept nil per oral at least 6 hours prior to the surgery.

On the day of surgery, patient’s identification, consent form, diagnosis were rechecked and confirmed. Inside the operation theater, standard monitors (Mindray A5, monitor) were attached to the patients. Systolic blood pressure (SBP), Diastolic blood pressure (DBP), mean arterial pressure (MAP), electrocardiogram, heart rate (HR), respiratory rate and pulse oximetry (SpO2) were monitored. Intravenous line was opened by appropriate size cannula. Intravenous crystalloid fluid was started.

Preoxygenation was done with 100% oxygen for 3 mins. Inj. Midazolam 0.04 mg/kg was given followed by Inj. Fentanyl 2 mcg/kg. Induction was carried out with Propofol in titrating dose till the loss of eyelash reflex. The muscle relaxant Inj. Vecuronium 0.1 mg/kg was given. Mask ventilation with oxygen and Isoflurane at 1% was continued for 3 mins. After 3 mins, laryngoscopy was performed using a Macintosh laryngoscope blade of appropriate size. Tracheal intubation was done with cuffed endotracheal tube of internal diameter 7.5 mm for male and 7.0 mm for female. Endotracheal tube was fixed after confirmation of placement of tube by EtCO2 (end tidal carbon dioxide) and chest auscultation. General anaesthesia was maintained using oxygen, Isoflurane, Vecuronium and IPPV (Intermittent Positive Pressure Ventilation).

Patients were randomly allocated into two groups using the 85 opaque sealed envelopes with code. Trained personnel (nurse not involved in the research) prepared the opaque envelope with code and the drug as per the allocation group. Group D-Dexmedetomidine group (n=42) and Group N-Normal saline group (n=43).

Anticipated ten mins before the end of the anaesthesia, Group D received intravenous dexmedetomidine 0.5 mcg/kg dissolved in normal saline to prepare 10 ml drug solution and Group N received 10 ml normal saline over 10 mins. Drug administration was done by the nurse in the operation theater and researcher (unknown to the drug identities) observed the outcome.

At the end of the study drug administration, Isoflurane was discontinued. Once patient starts breathing spontaneously, residual muscle relaxation was reversed with Inj. Neostigmine 0.05 mg/kg and Inj. Glycopyrrolate 0.01 mg/kg intravenously. Tracheal extubation was performed when the patient’s tidal volume reached at least 5-6 ml/kg. Oropharyngeal suctioning was done before extubation. After extubation 100% oxygen was given via facemask during recovery period.

Heart rate and mean arterial pressure were recorded just before the start of drug administration (considered as baseline value) then 1 min, 3 min, 5 min, 10 min of drug administration, at the time of extubation then 1 min, 3 min, 5 min, 10 min after extubation.

Any possible side effects of study drugs such as bradycardia and hypotension were recorded and managed as per the institute protocol. Bradycardia was defined as HR < 50 beats per min and hypotension was defined as MAP < 60 or SBP < 90 mmHg.

Extubation time was defined as time interval between cessation of anesthetic and tracheal extubation. Coughing was assessed at extubation with a 4-point scale at extubation:- 1: no coughing, 2: minimal coughing (once or twice), 3: moderate coughing (3—4 times) and 4: severe coughing (5 or more times).
Collected data were analyzed by means of various statistical tests. Independent t-test was used for comparison between two groups for continuous variables like age, weight, heart rate, mean arterial pressure and time to extubation. Chi square test or Fisher’s Exact test was used to analyse gender, ASA, coughing and incidence of adverse effect.

Results
Eighty five patients of ASA I and II were included in the study. Details in Consort flowchart. The age, gender, weight, ASA physical status and duration of surgery were comparable between the groups (Table 1).

Consort Flowchart:

- **Assessed for eligibility** (n=115)
  - Excluded (n = 30)
    - Not meeting inclusion criteria (n =18)
    - Refused to participate (n = 12)
  - Randomized (n = 85)
    - Allocated to intervention Group D (n = 42)
      - Received allocated intervention (n=40)
      - Did not receive allocated intervention (n=2)
    - Allocated to intervention Group N (n = 43)
      - Received allocated intervention (n=40)
      - Did not receive allocated intervention (n=3)
    - Discontinue intervention: (n=0)
    - Discontinue intervention: (n=0)
    - Analyzed (n = 40)
    - Analyzed (n = 40)
    - Excluded from analysis (n =0)
    - Excluded from analysis (n =0)
Table 1 Demographic Data of the patients in two study groups

| Variables                      | Group D (Mean±SD) | Group N (Mean±SD) | Test of significance (p-value) |
|-------------------------------|-------------------|-------------------|-------------------------------|
| Age (yrs)                     | 36.13±10.1        | 38.58±10.9        | 0.30                          |
| Gender (M/ F)                 | 15/25             | 14/26             | 0.82                          |
| Weight (kg)                   | 56.20±6.93        | 55.90±9.34        | 0.87                          |
| ASA I /II                     | 32/8              | 30/10             | 0.79                          |
| Duration of Surgery (mins)    | 95.13±18.0        | 92.25±18.5        | 0.48                          |

The mean HR and MAP prior to drug administration (T0) were comparable between the two groups. A statistical significance difference were observed in mean HR and MAP from 5min of drug administration till 10mins after extubation (Figure 1 and 2). Incidence of cough was assessed during extubation. Using 4 point coughing scale, 50% of Group N and 10% of Group D had minimal cough; 22.5% of Group N and 2.5% of Group D had moderate cough (Table 2). Incidence of bradycardia and hypotension was observed in Group D, 4 (10%) of the patient had bradycardia and 6 (15%) of the patient had hypotension (Table 3).

Time to extubation was statistically prolonged in Group D 7.61±2.41 mins compared to Group N 6.70±1.78 mins (p-value 0.049).

Figure 2. Comparison of mean arterial pressure (mean±SD) at different time between the study groups; * p-value < 0.01. Measurement points:- T0: prior to drug administration, T1: 1min of drug administration, T2: 3 mins of drug administration, T3: 5 mins of drug administration, T4: 10 mins of drug administration, T5: at extubation, T6: 1 min after extubation, T7: 3 mins after extubation, T8: 5 mins after extubation, T9: 10 mins after extubation

Table 2. Four point coughing scale
| Group   | Score 1 | Score 2 | Score 3 | Score 4 |
|---------|---------|---------|---------|---------|
|         | n      | %      | n      | %      | N   | %   | n  | %  |
| Group D | 35     | 87.5   | 4      | 10     | 1   | 2.5 | 0  | 0   |
| Group N | 11     | 27.5   | 20     | 50     | 9   | 22.5| 0  | 0   |

Table 3. Adverse effects

| Adverse Effects | Group D | Group N |
|-----------------|---------|---------|
|                 | n      | %      | n    | %    |
| Bradycardia     | 4      | 10     | 0    | 0    |
| Hypotension     | 6      | 15     | 0    | 0    |

Discussion

Tracheal extubation is associated with significant hemodynamic and airway responses. Although, these responses are usually transient, but its potential deleterious events cannot be ignored. Coughing during tracheal extubation is not only unpleasant but can also be harmful. It can cause abrupt increase in arterial pressure, heart rate and intracavitary pressure. Thus, various methods regarding prevention of this hemodynamic response to tracheal extubation have been suggested but none of them are completely successful. Dexmedetomidine is one of the drug now being practiced for the attenuation of the extubation reflex with good result. Dexmedetomidine has been used in this study to attenuate the tachycardia during extubation. The mean heart rate prior to study drug administration were comparable with p-value of 0.73. At the time of extubation and in the entire time interval after extubation, there was significant attenuation of the heart rate in the study group compared to control group (p-value <0.001). The result of this study shows that the administration of dexmedetomidine 0.5 mcg/kg intravenous over 10 mins before extubation significantly attenuates the hemodynamic and airway responses during extubation with side effects like bradycardia and hypotension compared to placebo. Guler et al\textsuperscript{12} and Turan et al\textsuperscript{14} used 0.5 mcg/kg dexmedetomidine over 60 sec, 5 mins before end of surgery and found significant attenuation of hemodynamic and airway responses during extubation with dexmedetomidine. Similar results were observed in the study conducted by Bindu B. et al\textsuperscript{11} and Ravi Shankar Goarya\textsuperscript{4} with higher dose of dexmedetomidine infusion ( 0.75 mcg/kg and 0.7 mcg/kg respectively). Dutta D. et al\textsuperscript{15} used 0.3 mcg/kg of dexmedetomidine over 60 sec before extubation and found significant attenuation (p-value <0.05) in HR and MAP from 2 min after drug administration till the end of the study.

In this study, four patients (10%) had bradycardia and six patients (15%) had hypotension in Group D compared to none in Group N. Bradycardia was treated with Inj. Atropine 0.01 mg/kg intravenous. Hypotension was managed initially with intravenous crystalloid and titrating the inhalational agent. Total number of four patient whose hypotension was not managed despite of fluid and titration of inhalational agent were given Mepheternine 6 mg bolus. Shruthi AH et al\textsuperscript{16} also observed similar increase in incidence of hypotension (22.5%) in dexmedetomidine group compared to none in control group. Incidence of bradycardia was 5% in their dexmedetomidine group compared to none in control group. In their, all the patients were premedicated with glycopyrrolate 5mcg/kg. In a study by Guler et al\textsuperscript{12}, 3.33% of patient had bradycardia and 10% of patient had hypotension in dexmedetomidine group compared to none in placebo group. In their study, all the patients were premedicated with atropine. Increased incidence of bradycardia (52%) in the study by Bindu B. et al\textsuperscript{11} could be due to increased dose of dexmedetomidine (0.75 mcg/kg). Dexmedetomidine induced reduction of heart rate and blood pressure is mainly dose dependent. Dutta D. et al\textsuperscript{15} observed no incidence of bradycardia and hypotension in their study.
with the use of dexmedetomidine 0.3 mcg/kg. In their study they have premedicated all the patients with Glycopyrrolate 0.2mg.

In this study, time to extubation was prolonged clinically in Group D compared to Group N. This was also statistically significant with p-value of 0.049. Lee JS et al. observed similar delay in time to extubation with dexmedetomidine 0.5 mcg/kg. In their study, time to extubation in dexmedetomidine group was 10 mins and in placebo group was 7 mins with p-value of < 0.001. Similarly, Shruthi et al. observed significantly prolonged time to extubation with dexmedetomidine 0.5 mcg/kg. In their study, time to extubation in dexmedetomidine group was 18.70±3.36 mins while in control group, it was 15.24±1.60 mins (p-value <0.001)

Limitations: This study was conducted taking general population undergoing various surgery rather than specific surgery. As ASA I and II patients were only included in the study, the implication of mentioned study in other cohorts of patient (ASA III and IV) could be different. Cases managed with atropine and mephenetermine were also included in the study, which would have affected the result. Train of four count for reversal of neuromuscular blocker was not monitored. Postoperative sedation was not recorded.

This study concludes that intravenous dexmedetomidine 0.5 mcg/kg before extubation significantly attenuates the hemodynamic and airway responses to extubation with prolonged time for extubation and with side effects like bradycardia and hypotension compared to placebo.

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Conflict of interests:

The authors have filled the ICMJE COI form and state that they have nothing to disclose. Dr Achyut Sharma is editor of this journal and he did not participate in editorial decision making of this article.

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