

The effect of two different doses of dexmedetomidine to attenuate cardiovascular and airway responses to tracheal extubation: a double blind randomized controlled trial

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Abstract

Background: The objective of the study is to assess the effectiveness of two different doses of dexmedetomidine, an alpha 2 adrenergic agonist, to attenuate the cardiovascular and airway responses to tracheal extubation and to observe the adverse effects. **Methodology:** Ninety ASA grade I and II patients aged 18-50 years were randomized into three groups; A, B, and C to receive dexmedetomidine 0.5µg/kg, 1µg/kg and normal saline placebo respectively about 15 minutes before discontinuation of inhalational agent. The heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were recorded during administration of drug, before extubation, during extubation, at 1, 3 minutes and every 5 minutes thereafter. Extubation quality was assessed on a 5 point scale and sedation by Ramsay sedation score. **Results:** There was significant decrease in heart rate and mean arterial pressure ($p < 0.001$) during extubation in group A and B. Ninety percent of patients in group A, 93.3% patients in group B and 16.7% in group C could be extubated smoothly. The average time to extubate was 12.13 ± 2.11 , 14.08 ± 3.19 and 10.27 ± 2.09 minutes in groups A, B, and C respectively (P value < 0.001). Higher incidence of bradycardia ($p < 0.001$) was observed in Group A and B whereas incidence of breath holding was higher in group C ($p = 0.024$). **Conclusion:** A dose of 0.5µg/kg of dexmedetomidine administered as a bolus infusion before extubation attenuates the stress response to extubation as effectively as 1µg/kg. Higher sedation scores and longer time to extubate are seen with a dose of 1µg/kg without causing respiratory depression.

Key words: Bradycardia, Breath holding, Dexmedetomidine, Respiratory depression, Tracheal extubation.

Introduction

Tracheal extubation is performed at the end of surgical procedure when the patient is fully awake and is able to protect his airway. Extubation may be associated with upper airway obstruction, laryngospasm, bronchospasm, tachycardia, hypertension and dysrhythmias [1-3]. This may lead to complications like hypoventilation, pulmonary aspiration, wound disruption, pulmonary edema, increase in plasma concentrations of catecholamines, rise in intracranial and intraocular

pressures and myocardial ischemia in susceptible individuals [3-7]. A smooth extubation without straining, movement, laryngospasm or coughing helps in avoiding these complications. Another problem upon emergence from general anesthesia is emergence delirium which is significantly related to the anesthetic agents used and the duration of the procedure. This may lead to injuries, pain, hemorrhage, self extubation and removal of catheters [9,10]. Many techniques like use of LMA (laryngeal mask airway) during emergence [11], extubation in deep plane of anesthesia and drugs like lignocaine, opioids, calcium channel blockers,

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magnesium sulphate, propofol and esmolol have been used to attenuate the cardiac and airway responses to extubation [12]. Opioids, analgesics, benzodiazepines, propofol and clonidine have been used to control emergence agitation in pediatric age group [13-16]. None of them have been found completely successful.

Adrenergic alpha 2 agonists seem to have the ability to attenuate the pressor response to intubation and extubation [17]. Clonidine has been used for attenuation of stress responses, hypertension and to treat narcotic withdrawal symptoms [18-20]. Dexmedetomidine is a selective adrenergic α_2 agonist with α_2 : α_1 selectivity of 1620:1 compared to 220:1 for Clonidine [21]. It has sedative, analgesic and anesthetic sparing effects and it decreases heart rate, blood pressure and circulating plasma catecholamines in a dose dependent fashion [22-25]. It sedates patients by decreasing central sympathetic activity and they are easily roused to full consciousness [26]. Agitation seen along with GABA (Gamma Amino Butyric Acid) related sedatives is not seen with dexmedetomidine [27] and it does not affect respiratory rate, CO₂ clearance and may improve oxygenation [28,29]. Lack of respiratory depression, arousable sedation and hemodynamic stability makes dexmedetomidine a better choice to attenuate the pressor response to extubation with an added advantage of preventing emergence delirium [30,31]. Different concentrations of dexmedetomidine ranging from 0.25 $\mu\text{g}/\text{kg}$ to 1.0 $\mu\text{g}/\text{kg}$ IV as a bolus, have been studied for attenuation of pressor responses to extubation and intubation [17,32-34].

The objective of the study is to assess the effectiveness of two different doses of dexmedetomidine to attenuate the cardiovascular and airway responses to tracheal extubation and to observe the adverse effects, if any. The null hypothesis states that the administration of dexmedetomidine as a bolus dose over 10 minutes before the end of surgery does not help in attenuation of cardiovascular and airway reflex responses to extubation.

Operational definitions include: bradycardia - defined as a heart rate less than 60 per minute; breath holding - holding breath for more than 20 seconds; hypertension - systolic blood pressure more than 180mmHg; hypotension - a decrease in systolic blood pressure 25% below the baseline value; respiratory depression - respiratory rate less than 14 per minute in the absence of laryngospasm or bronchospasm; tachycardia - heart rate more than or equal to 100 persisting for more than

3 minutes; time to extubate - time from discontinuation of inhalational agent to extubation.

Material and Methods

This is a double blinded prospective randomized comparative study. The duration of the study was one and a half years. Both males and females of ASA physical status I and II in the age group 18-50 years were included. The exclusion criteria were patient refusal, patients with a history of allergy to multiple drugs, patients with history of drug/ alcohol abuse and pregnant or lactating women. After institutional ethical committee clearance and getting informed written consent, 90 patients undergoing elective surgical procedures of spine, lasting for more than 120 minutes were randomized into three groups, A, B and C of 30 each by a sealed envelope method. Each group received intravenous infusion of the drug or placebo solution as follows. Group A – dexmedetomidine 0.5 $\mu\text{g}/\text{kg}$; Group B - dexmedetomidine 1 $\mu\text{g}/\text{kg}$; Group C - Normal Saline (NS) placebo.

Pre-anesthetic checkup was conducted and a written informed consent was obtained from each patient. Baseline investigations and screening tests were done. Tab. Ranitidine 150mg, Tab. Metoclopramide 10mg and Tab. Alprazolam 0.25mg were given orally on previous night before surgery and at one hour prior to surgery with a sip of water. On the day of surgery, basal heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), peripheral oxygen saturation (SpO₂), respiratory rate (RR) and continuous ECG monitoring were recorded after connecting multiparameter monitor. A peripheral intravenous line with 18 gauge cannula was secured in one of the upper limbs. Patients were premedicated with injection glycopyrrolate 0.004mg/kg intravenous (IV), injection midazolam 1mg IV (titrated to the desired sedation in incremental doses of 0.5mg IV) and injection fentanyl 1 $\mu\text{g}/\text{kg}$ IV.

All patients received a standardized general anesthesia. Preoxygenation was followed by induction with propofol 2.5 mg/kg and vecuronium 0.1mg/kg to facilitate tracheal intubation. Anesthesia was maintained with Isoflurane 0.6-1.0% vaporized in 66% N₂O & 34% oxygen by IPPV (Intermittent positive pressure ventilation). Injection paracetamol 1g IV was given over 15 minutes to provide analgesia. Test solutions were prepared as follows: solution A – dexmedetomidine 50 $\mu\text{g}/100\text{ml}$ of NS (0.5 $\mu\text{g}/\text{ml}$);

solution B – dexmedetomidine 100 µg/ 100ml of NS (1µg/ml) and solution C - 100 ml of NS.

About 15 minutes before discontinuation of inhalational anesthetic agent, each patient received 1ml/ kg of the specified test solution which was not known to the anesthesiologist as an IV infusion over 10minutes. HR, SBP, DBP, MAP, RR and SpO₂ were recorded just before administration of test solution and thereafter at 1, 3, 5, 10 and 15 minutes. Residual neuromuscular blockade was reversed by Neostigmine 50µg/kg and Glycopyrrolate 10µg/kg, once the patients started spontaneous breaths. When the spontaneous respirations were adequate and patients were able to obey simple commands, suction of the throat was done and tracheal extubation was performed. HR, SBP, DBP, MAP, SpO₂ and RR were recorded one minute before extubation, during extubation, and at 1, 3, 5, 10, 15, 20, & 30 minutes after extubation. Time to extubate was recorded. The occurrence of coughing or gagging, breath holding, laryngospasm, bronchospasm, emergence delirium and undue sedation were also recorded. Hypotension was corrected by IV fluids and

injection mephentermine 3mg IV if required. Bradycardia was corrected, if associated with hemodynamic instability with atropine 0.5mg IV. Quality of extubation was evaluated based on cough immediately after extubation; using a 5 point scale [35].

- 1= No coughing
- 2= Smooth extubation, minimal coughing (1-2 times)
- 3= Moderate coughing (3-4 times)
- 4= Severe coughing (5-10 times)
- 5= Poor extubation (laryngospasm / coughing >10 times)

Postoperative sedation was assessed on a 6 point scale (Ramsay scale) on arrival at PACU [37].

- 1= Anxious or agitated and restless or both
- 2= Cooperative, oriented and tranquil
- 3= Drowsy but responds to commands
- 4= Asleep, brisk response to light glabellar tap or loud auditory stimulus
- 5= Asleep, sluggish response to light glabellar tap or loud auditory stimulus
- 6= Asleep and unarousable

Analysis and Results

The statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 have been used for the analysis of the data. Descriptive and inferential statistical analysis has been carried out in the study. Continuous measurements are presented on mean ± SD (Min-Max). Categorical measurements are presented in number (%). Significance is assessed at 5 % level of significance.

The following assumptions on data were made; 1. dependent variables should be normally distributed 2. samples drawn from the population should be random, and cases of the samples should be independent. Analysis of variance (ANOVA) has been used to find the significance of study parameters between three groups of patients.

Post-Hoc Tukey test has been used to find the pair wise significance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. P value ≤ 0.05 has been considered as statistically significant.

Patients in the study groups were comparable with reference to age. The mean age in group A, B, and C were 34.37±8.56, 35.33±9.29 and 36.30±8.50 respectively with a P value of 0.697 [table 1]. The male: female ratio was 22:8, 21:9 and 20:10 in groups A, B, and C respectively with a P value of 0.853; showing comparable gender distribution between the groups [table 2].

The types of surgery included cervical (30%, 33.3%, 40% in groups A, B, C respectively), thoracic (6.7%, 6.7%, 10% in groups A, B, C respectively) and lumbar (63.3%, 60%, 50% in groups A,B,C respectively) spine surgeries and were comparable between the groups [table 3].

The average duration of surgery was 173.30±27.29, 169.93±23.03 and 171.73±22.29 minutes in groups A, B, and C respectively which was comparable, with a P value of 0.866. No statistically significant differences were observed in the baseline hemodynamic parameters including HR (P value 0.746), SBP (P value 0.894), DBP (P value 0.195) and MAP (P value 0.398) in the three groups [figures 1-4].

Table-1: Age distribution of patients.

Age in years	Group A†		Group B‡		Group C§	
	No	%	No	%	No	%
<20	2	6.7	2	6.7	0	0.0
20-30	9	30.0	7	23.3	9	30.0
31-40	11	36.7	12	40.0	12	40.0
41-50	8	26.7	9	30.0	9	30.0
Total	30	100.0	30	100.0	30	100.0
Mean ± SD	34.37±8.56		35.33±9.29		36.30±8.50	

*data are expressed as mean± standard deviation, P=0.697. †Group A – dexmedetomidine 0.5 µg/kg, ‡Group B - dexmedetomidine1µg/kg, §Group C - normal saline placebo.

Table-2: Gender distribution of patients.

Gender	Group A†		Group B‡		Group C§	
	No	%	No	%	No	%
Male	22	73.3	21	70.0	20	66.7
Female	8	26.7	9	30.0	10	33.3
Total	30	100.0	30	100.0	30	100.0

*data are expressed as mean± standard deviation, P=0.853. †Group A – dexmedetomidine 0.5 µg/kg, ‡Group B - dexmedetomidine1µg/kg, §Group C - normal saline placebo.

Table-3: Comparison of types of surgical procedure in study groups.

Surgery	Group A†		Group B‡		Group C§	
	No	%	No	%	No	%
1.Thoracic spine procedures	2	6.7	2	6.7	3	10
2.Cervical spine procedures	9	30.0	10	33.3	12	40.0
3.Lumbar spine procedures	19	63.3	18	60.0	15	50.0
Total	30	100.0	30	100.0	30	100.0

* data is presented in number (%). †Group A – dexmedetomidine 0.5 µg/kg, ‡Group B - dexmedetomidine1µg/kg, §Group C - normal saline placebo.

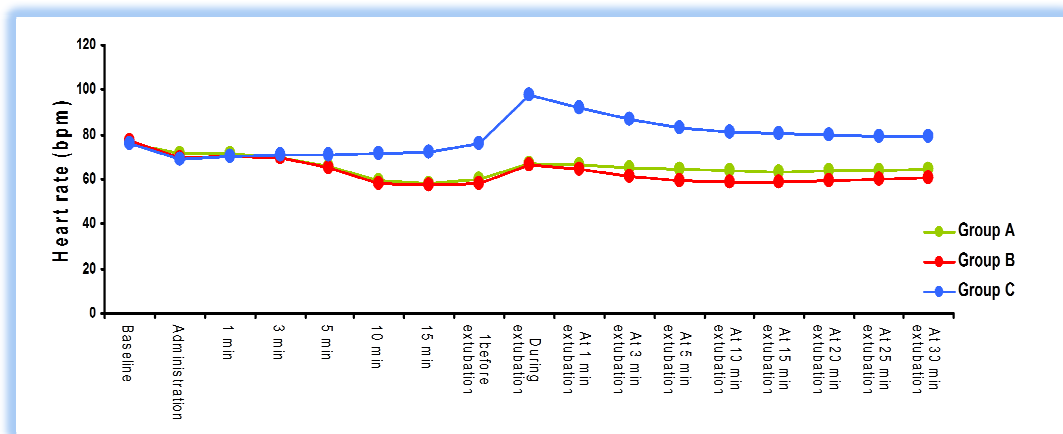


Figure-1: Comparison of HR variation in the groups

*Group A – dexmedetomidine 0.5 µg/kg, †Group B - dexmedetomidine1µg/kg, ‡Group C - normal saline placebo.

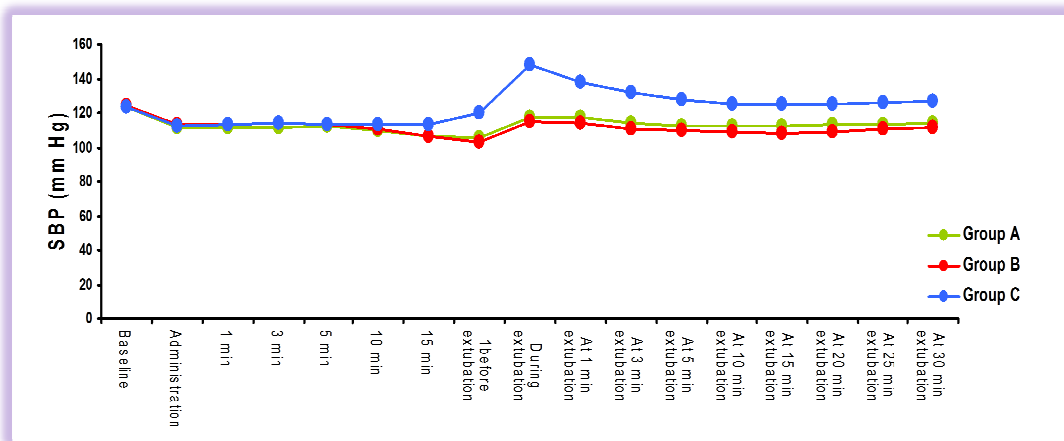


Figure-2: Comparison of SBP variation in study groups

*Group A – dexmedetomidine 0.5 µg/kg, †Group B - dexmedetomidine 1µg/kg, ‡Group C - normal saline placebo.
§SBP- Systolic Blood Pressure

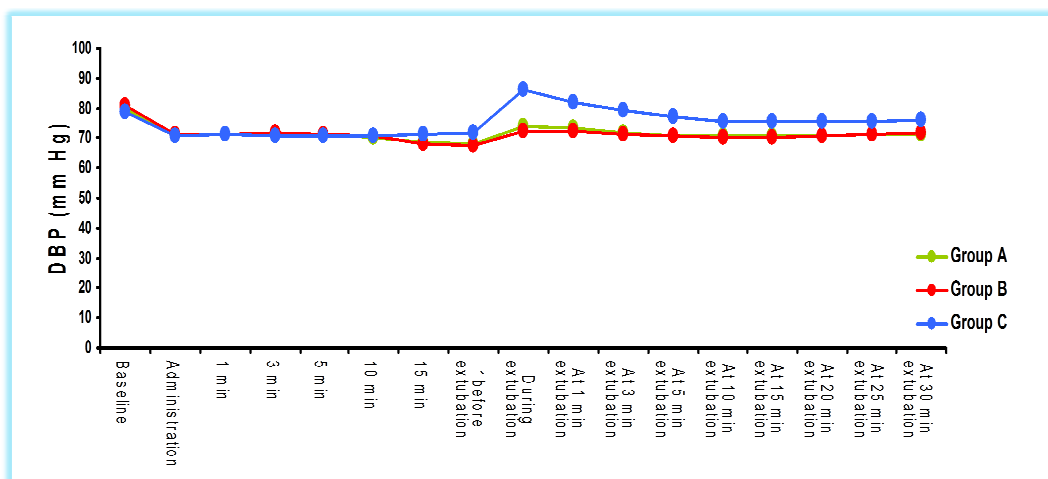


Figure 3: Comparison of DBP variation in study groups

*Group A – dexmedetomidine 0.5 µg/kg, †Group B - dexmedetomidine 1µg/kg, ‡Group C - normal saline placebo.
§DBP- Diastolic Blood Pressure

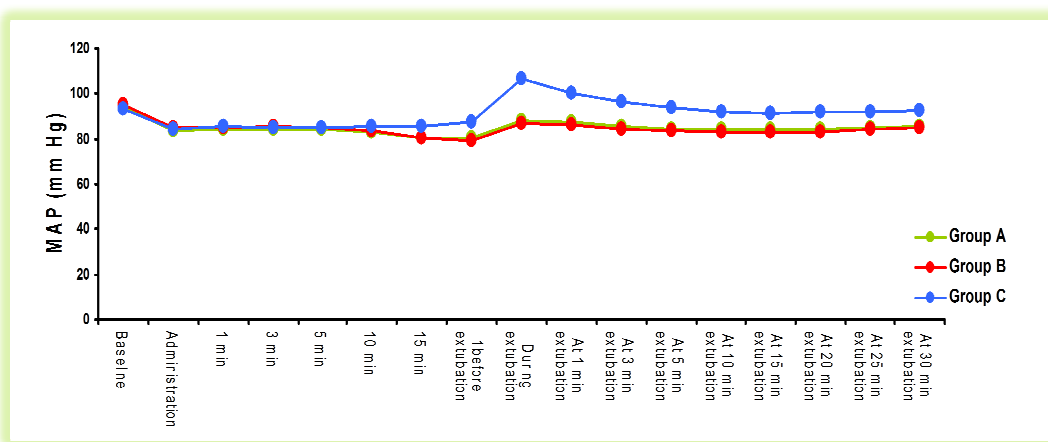


Figure-4: Comparison of MAP variation in study groups.

*Group A – dexmedetomidine 0.5 µg/kg, †Group B - dexmedetomidine 1µg/kg, ‡Group C - normal saline placebo.
§MAP – Mean Arterial Pressure.

No significant difference was observed in HR before administration of the drug (P value =0.431), at 1 minute (P value=0.726) and at 3minutes (P value=0.768) after starting the bolus dose. A statistically significant difference was observed in HR from 5minutes after starting the bolus dose (P value=0.002) till 30 minutes after extubation (P value<0.001). Pair wise analysis also showed a significant difference between groups A & C as well as Group B & C from 5minutes after administration (P values of 0.015 and 0.002 respectively) till 30 minutes after extubation (P values of <0.001, <0.001 respectively). No significant difference was observed between Groups A & B from starting of drug (P value=0.593) till 3 minutes after extubation (P value<0.088) but a significant difference thereafter till 25 minutes of extubation [figure 1].

SBP showed no significant difference from the time before administration (P value=0.715) up to 10 minutes (P value=0.137) after starting the drug; whereas a strongly significant difference was noticed from 15 minutes of drug administration (P value<0.001) till 30 minutes after extubation (P value<0.001). Pair wise analysis also showed strongly significant difference (P value<0.001) in groups A & C and B & C from 15minutes of administration till 30 minutes after extubation; but groups A & B showed no significant difference in SBP variation [figure 2]. DBP showed no significant difference from the time before administration (P value =0.894), up to 10 minutes (P value =0.991) after starting the drug. There was suggested significance at 15 minutes (P value =0.081), moderate significance at 1 minute before extubation (P value =0.018) and strongly significant difference from time of extubation (P value<0.001) till 30 minutes after extubation (P value <0.001). Pair wise analysis also showed significant difference in groups A & C and B & C from 1minute before (P value =0.048;0.027 respectively), through extubation (P value <0.001), till 30 minutes after extubation (P value =0.002; 0.003 respectively); but groups A & B showed no significant difference in DBP throughout [figure 3].

No significant difference was observed in MAP from the time before administration (P value = 0.879) up to 10 minutes (P value =0.308) after starting the drug; whereas strongly significant difference was observed from 15 minutes (P value =0.001) after drug administration, through the time of extubation (P value <0.001) till 30 minutes after extubation (P value <0.001). Pair wise analysis also showed significant difference (P value <0.001) in groups A & C and B & C from 15 minutes of administration, during extubation and till 30 minutes after extubation; but groups A & B showed no significant difference in MAP throughout [figure 4].

Ninety percent of patients in group A could be extubated smoothly with no or minimal cough (scores 1or 2) whereas 10.0% had moderate cough (score 3). Majority of patients (93.3%) in group B had a smooth extubation with scores 1 and 2 whereas 6.6% had a score of 3. In group C only 16.7% had extubation scores of 1or 2, 50% had moderate cough (score 3), 26.7% had severe cough and 6.7% had a poor quality extubation (score 5). There was a significant difference in the quality of extubation with P value < 0.001 [table 4]. The average time to extubate was 12.13±2.11, 14.08±3.19 and 10.27±2.09 minutes in groups A, B, and C respectively showing a statistically significant difference (P value <0.001). It was observed that 60% of patients in group A and 83.3% in group C could be extubated within 1-12 minutes after discontinuation of inhalational agent whereas extubation could be performed in only 26.7% of group B patients within 12 minutes [table 5].

Table-4: Comparison of extubation quality in study groups.

Extubation quality†	Group A‡		Group B§		Group C	
	No	%	No	%	No	%
1	3	10.0	6	20.0	0	0.0
2	24	80.0	22	73.3	5	16.7
3	3	10.0	2	6.7	15	50.0
4	0	0.0	0	0.0	8	26.7
5	0	0.0	0	0.0	2	6.7
Total	30	100.0	30	100.0	30	100.0

* data is presented in number †1= no coughing, 2= smooth extubation, minimal coughing (1-2 times), 3= moderate coughing (3-4 times), 4= severe coughing (5-10 times), 5= poor extubation (laryngospasm / coughing >10 times).
‡Group A – dexmedetomidine 0.5 µg/kg, §Group B - dexmedetomidine 1µg/kg, ||Group C - normal saline placebo.

Table-5: Comparison of time to extubate (minutes) in study groups.

Time extubate (min)	Group A†		Group B‡		Group C§	
	No	%	No	%	No	%
1-12	18	60.0	8	26.7	25	83.3
13-24	12	40.0	22	73.3	5	16.7
Total	30	100.0	30	100.0	30	100.0
Mean ± SD	12.13±2.11		14.80±3.19		10.27±2.09	

*data are expressed as mean± standard deviation, = P < 0.001. †Group A – dexmedetomidine 0.5 µg/kg, ‡Group B - dexmedetomidine 1µg/kg, §Group C - normal saline placebo.

On assessment of sedation scores, it was observed that 3.3% patients in group A, nil in group B and 10% in group C were found anxious and restless (Ramsay score 1). Those who were cooperative, oriented and tranquil (Ramsay score 2) accounted for 20%, 13.3% and 63.3% in groups A, B and C respectively. Majority of patients in group A and B had a sedation score of 3 i.e. 73.3% and 66.7% respectively; while only 26.7% in group C. A high sedation score of 4 was observed in 20% of patients in group B, 3.3% in group A and no one in group C. Sedation scores above 4 was not observed in any of the patients [table 6].

Table-6: Comparison of sedation score in study groups.

Sedation score†	Group A‡		Group B§		Group C	
	No	%	No	%	No	%
1	1	3.3	0	0.0	3	10.0
2	6	20.0	4	13.3	19	63.3
3	22	73.3	20	66.7	8	26.7
4	1	3.3	6	20.0	0	0.0
5	0	0.0	0	0.0	0	0.0
6	0	0.0	0	0.0	0	0.0
Total	30	100.0	30	100.0	30	100.0

* data is presented in number (%). †1= anxious or agitated and restless or both, 2= cooperative, oriented and tranquil, 3= drowsy but responds to commands, 4= asleep, brisk response to light glabellar tap or loud auditory stimulus, 5= asleep, sluggish response to light glabellar tap or loud auditory stimulus, 6= asleep and unarousable. ‡Group A – dexmedetomidine 0.5 µg/kg, §Group B - dexmedetomidine 1µg/kg, ||Group C - normal saline placebo.

Table-7: Comparison of side effects in study groups.

Side effects	Group A† (n=30)		Group B‡ (n=30)		Group C§ (n=30)		P value
	No	%	No	%	No	%	
Bradycardia	17	56.7	20	66.7	1	3.3	<0.001
Hypotension	3	10.0	4	13.3	0	0.0	0.133
Breath holding	1	3.3	0	0.0	5	16.7	0.024
Emergence delirium	0	0.0	0	0.0	0	0.0	-

*data is presented in number (%). †Group A – dexmedetomidine 0.5 µg/kg ‡Group B - dexmedetomidine 1µg/kg §Group C - normal saline placebo.

The incidence of bradycardia was higher in groups A and B (56.7% and 66.7% respectively) compared to group C (3.3%) with a P value of <0.001. None was associated with hemodynamic instability and required no treatment. Hypotension was seen in 10% of group A patients, 13.3% in group B and no one in group C which was statistically not significant (P=0.133). Breath holding was observed in 3.3% in group A, 16.7% in group C and none in group B with a P value of 0.024 showing moderate significance. None of the patients experienced emergence delirium [table 7].

Discussion

Hemodynamic changes associated with tracheal extubation may be due to pain, emergence from anesthesia, changes in plasma catecholamine levels or tracheal irritation [37,38]. These hemodynamic changes normally do not constitute a major problem; but could be deleterious in patients with comorbidities [5,7,39,40].

Dexmedetomidine activates the medullary vasomotor centre receptors, reducing central sympathetic outflow, resulting in decreased heart rate and blood pressure. Different studies have shown desirable as well as undesirable hemodynamic changes with doses ranging from 0.25µg/kg -1.0µg/kg as intravascular infusion [17,32-34,41]. In the present study a significant reduction in HR was observed from 5minutes after starting infusion in both 0.5µg/kg and 1.0µg/kg groups; with attenuation of rise in HR during extubation. Both doses effectively controlled responses in HR to extubation but the mean HR was significantly lower in 1µg/kg group from 5minutes after extubation till 30 minutes when compared with 0.5µg/kg group. The incidence of bradycardia was comparable between the two doses and none required treatment with atropine. In the present study, the SBP, DBP and MAP were significantly stable during extubation with both 0.5µg/kg and 1.0µg/kg groups when compared with the placebo group, without causing significant hypotension. Both doses were found to be effective in attenuating the hemodynamic responses to extubation.

Most of the patients who received dexmedetomidine could be extubated with an extubation quality score of 1 or 2; whereas the in the placebo group, 50% had moderate cough, 26.7% had severe cough and 6.7% had a poor extubation with laryngospasm. The incidence of breath holding was also significantly reduced in both 0.5µg/kg and 1.0µg/kg groups when compared to placebo group. There was no associated respiratory depression seen in patients who received dexmedetomidine in either group.

The observations in the present study are comparable with the results of the study done by Guler G et al [17] suggesting a less significant increase in HR, SBP and DBP in response to extubation with 0.5µg/kg single bolus dose of, given as a slow IV infusion 5 minutes before the end of the surgery. They also suggested a better quality of extubation with without causing any respiratory depression. In contrast to the present study

they suggested a comparable incidence of breath holding. Similar findings have been made by Aksu R et al [32] where 0.5µg/kg intravenous bolus infusion of dexmedetomidine given at the end of surgery effectively attenuated airway reflex responses to extubation maintaining good hemodynamic stability compared with 1µg/kg of fentanyl. They observed that no patient in the dexmedetomidine group experienced severe coughing or laryngospasm whereas 20% had severe coughing and 5% had laryngospasm in Fentanyl group. Dexmedetomidine 0.5µg/kg administered 5 minutes before surgery has been shown to stabilize hemodynamic, allow easy extubation and allow early neurological examination following intracranial operations in a study done by Turan G et al [35]; which supports present results. Guler G et al [42] suggested 0.5µg/kg of dexmedetomidine 5 minutes before end of surgery resulted in less number of severe coughs per patient, significant reduction in breath holding, no respiratory depression and better hemodynamic stability compared to placebo without adverse effects like laryngospasm, bronchospasm, hypotension or bradycardia. Talke P et al [43] observed that in patients undergoing vascular surgery, dexmedetomidine effectively attenuated the rise in HR and plasma catecholamine levels during emergence from anesthesia. Ibacache et al [44] reported no reduction in HR with at a lower dose of 0.3µg/kg but MAP showed significant reduction and significant reduction in agitation in pediatric patients after sevoflurane anesthesia.

The time to extubate was found to be significantly prolonged in patients who received dexmedetomidine at 1µg/kg (extubation time \geq 13minutes in 73.3% of patients); whereas 40% of patients who received 0.5µg/kg and only 16.7% in placebo group had extubation time \geq 13 minutes. Similar findings have been made by Guler G et al [42] suggesting 0.5µg/kg of dexmedetomidine 5 minutes before the end of surgery significantly prolonged time to extubate. Kim Y S et al [45] observed prolonged extubation time with 0.75µg/kg and 1.0µg/kg administered as a bolus infusion over 10 minutes, 30 minutes before the end of the surgery compared with placebo; using desflurane for maintenance. Kim S Y et al [46] concluded that intraoperative infusion of dexmedetomidine (0.4µg /kg/ hour) provided smooth and aerodynamically stable emergence; with improved quality of recovery after nasal surgery without significant prolongation of time to

extubate (desflurane was used for maintenance). In contrast to the observations made by the present study, there have been reports suggesting no significant difference in extubation times when compared to placebo [17] and Fentanyl 1 μ g/kg [32] as bolus dose 5 minutes before the end of surgery; both studies using sevoflurane as inhalational agent. Turan G et al [35] also suggested no significant difference in time to extubate in neurosurgical patients who received dexmedetomidine 0.5 μ g/kg, 5 minutes before the end of the surgery; using isoflurane for maintenance.

Central stimulation of parasympathetic outflow along with inhibition of sympathetic outflow from locus coeruleus in the brain stem plays a major role in the sedative and anxiolytic properties of dexmedetomidine. The sedation scores were assessed by Ramsay Scale. In the present study higher sedation scores were observed in patients who received dexmedetomidine. Majority of patients (73.3% and 66.7%) who received dexmedetomidine 0.5 μ g/kg and 1 μ g/kg respectively were drowsy but responding to commands. None of the patients had respiratory depression. Tanskanen P E et al [15] observed hemodynamic stability as well as arousable sedation without respiratory depression in patients who underwent intracranial tumor surgery with an infusion of starting 20 minutes before surgery and continuing till skin closure. Aksu et al [32] reported higher sedation scores in patients receiving 0.5 μ g/kg dexmedetomidine at the end of surgery without respiratory depression in patients who underwent rhinoplasty; in a comparative study with fentanyl. The lower frequency of airway complications in the group could be due to lesser degree of laryngeal irritation from sedative and analgesic properties of dexmedetomidine.

Significant bradycardia was observed in patients who received dexmedetomidine the incidence being higher with 1 μ g/kg dose. None of the cases were hemodynamically unstable and required no treatment. The incidence of hypotension was 10% and 13.3% in patients who received dexmedetomidine 1 μ g/kg and 0.5 μ g/kg respectively; without anyone in the placebo group developing hypotension. The incidence of breath holding was significantly higher in placebo group. The two different dosages did not differ significantly in their side effect profile except for higher sedation scores with 1 μ g/kg. There are studies suggesting 0.5 μ g/kg of dexmedetomidine 5 minutes before end of surgery significantly reduced the incidence of breath holding without causing hypotension, bradycardia, laryngospasm or respiratory depression [42].

Dexmedetomidine when used in morbidly obese patients has been found not to cause any respiratory depression [47]. Karaaslan K et al [48] have also reported higher incidence of bradycardia and hypotension in a comparative study of dexmedetomidine with midazolam for monitored anesthesia care in nasal endoscopy.

Conclusion

The present study concludes that a dose of 0.5 μ g/kg of dexmedetomidine administered as a bolus dose before extubation attenuates the stress response to extubation as effectively as 1 μ g/kg. Both doses maintain hemodynamic stability; enabling smooth extubation with significant reduction in cough, breath holding and laryngospasm. Dexmedetomidine provides adequate sedation in the post operative period without causing respiratory depression but causes prolongation of time to extubate; which is more with a dose of 1 μ g/kg.

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References

1. Peterson GN, Domino KB, Caplan RA, Posner KL, Lee LA, Cheney FW. Management of the difficult airway: a closed claims analysis. *Anesthesiology*. 2005 Jul;103(1):33-9.
2. Rex MA. A review of the structural and functional basis of laryngospasm and a discussion of the nerve pathways involved in the reflex and its clinical significance in man and animals. *British Journal of Anaesthesia*. 1970 Oct 1;42(10):891-9.
3. Hartley M, Vaughan RS. Problems associated with tracheal extubation. *Br J Anaesth*. 1993 Oct;71(4):561-8.
4. Padley SP, Downes MO. Case report: pulmonary oedema secondary to laryngospasm following general anaesthesia. *Br J Radiol*. 1994 Jul;67(799):654-5.
5. Lowrie A, Johnston PL, Fell D, Robinson SL. Cardiovascular and plasma catecholamine responses at tracheal extubation. *Br J Anaesth*. 1992 Mar;68(3):261-3.
6. Edwards N, Alford A, Dobson P, Reilly C. Myocardial ischemia during intubation and extubation. *British Journal of Anaesthesia*. 1994 Apr 1;72(4):483-84.

7. Barham NJ, Boomers OW, Sherry KM, Locke TJ. Myocardial ischaemia during tracheal extubation in patients after cardiac surgery: an observational study. *British journal of anaesthesia*. 1998 Jun 1;80(6):832-3.
8. Cranfield KA, Bromley LM. Minimum alveolar concentration of desflurane for tracheal extubation in deeply anaesthetized, unpremedicated children. *British journal of anaesthesia*. 1997 Apr 1;78(4): 370-1.
9. Lepoussé C, Lautner CA, Liu L, Gomis P, Leon A. Emergence delirium in adults in the post-anaesthesia care unit. *Br J Anaesth*. 2006 Jun;96(6):747-53. Epub 2006 May 2.
10. Rogers MP, Liang MH, Daltroy LH, Eaton H, Peteet J, Wright E, Albert M. Delirium after elective orthopedic surgery: risk factors and natural history. *The International Journal of Psychiatry in Medicine*. 1990 Jun 1;19(2):109-21.
11. Koga K, Asai T, Vaughan RS, Latto IP. Respiratory complications associated with tracheal extubation timing of tracheal extubation and use of the laryngeal mask during emergence from anaesthesia. *Anaesthesia*. 1998 Jun 1;53(6):540-4.
12. Gonzalez RM, Bjerke RJ, Drobycki T, Stapelfeldt WH, Green JM, Janowitz MJ, Clark M. Prevention of endotracheal tube-induced coughing during emergence from general anesthesia. *Anesthesia & Analgesia*. 1994 Oct 1;79(4):792-5.
13. Galinkin JL, Fazi LM, Cuy RM, Chiavacci RM, Kurth CD, Shah UK, Jacobs IN, Watcha MF. Use of intranasal fentanyl in children undergoing myringotomy and tube placement during halothane and sevoflurane anesthesia. *Anesthesiology*. 2000 Dec;93(6): 1378- 83.
14. Davis PJ, Greenberg JA, Gendelman M, Fertal K. Recovery characteristics of sevoflurane and halothane in preschool-aged children undergoing bilateral myringotomy and pressure equalization tube insertion. *Anesth Analg*. 1999 Jan;88(1):34-8.
15. Lapin SL, Auden SM, Goldsmith LJ, Reynolds AM. Effects of sevoflurane anaesthesia on recovery in children: a comparison with halothane. *Paediatr Anaesth*. 1999;9(4):299-304.
16. Kulka PJ, Bressemer M, Tryba M. Clonidine prevents sevoflurane-induced agitation in children. *Anesth Analg*. 2001 Aug;93(2):335-8, 2nd contents page.
17. Guler G, Akin A, Tosun Z, Eskitascoglu E, Mizrak A, Boyaci A. Single-dose dexmedetomidine attenuates airway and circulatory reflexes during extubation. *Acta anaesthesiologica scandinavica*. 2005 Sep 1;49(8):1088-91.
18. Bloor BC, Flacke WE. Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. *Anesth Analg*. 1982 Sep;61(9):741-5.
19. Pouttu J, Scheinin B, Rosenberg PH, Viinamäki O, Scheinin M. Oral premedication with clonidine: effects on stress responses during general anaesthesia. *Acta Anaesthesiol Scand*. 1987 Nov;31(8):730-4.
20. Gold MS, Redmond DE Jr, Kleber HD. Clonidine blocks acute opiate-withdrawal symptoms. *Lancet*. 1978 Sep 16;2(8090):599-602.
21. Virtanen R, Savola JM, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an alpha 2-adrenoceptor agonist. *Eur J Pharmacol*. 1988 May 20;150(1-2):9-14.
22. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. *Anesthesiology*. 1992 Dec;77(6):1125-33.
23. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology*. 1992 Dec;77(6):1134-42.
24. Aho M, Lehtinen AM, Erkola O, Kallio A, Korttila K. The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. *Anesthesiology*. 1991 Jun;74(6):997-1002.
25. Talke P, Richardson CA, Scheinin M, Fisher DM. Postoperative pharmacokinetics and sympatholytic effects of dexmedetomidine. *Anesthesia & Analgesia*. 1997 Nov 1;85(5):1136-42.
26. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesthesia & Analgesia*. 2000 Mar 1;90(3):699-705.

27. Shelly MP. Dexmedetomidine: a real innovation or more of the same? *Br J Anaesth*. 2001 Nov;87(5):677-8.
28. Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Crit Care*. 2000;4(5):302-8. Epub 2000 Jul 31.
29. Tanskanen PE, Kytta JV, Randell TT, Aantaa RE. Dexmedetomidine as an anaesthetic adjuvant in patients undergoing intracranial tumour surgery: a double-blind, randomized and placebo-controlled study. *British journal of anaesthesia*. 2006 Nov 1;97(5):658-65.
30. Carollo DS, Nossaman BD, Ramadhyani U. Dexmedetomidine: a review of clinical applications. *Curr Opin Anaesthesiol*. 2008 Aug;21(4):457-61. doi: 10.1097/ACO.0b013e328305e3ef.
31. Yazbek-Karam VG, Aouad MM. Perioperative uses of dexmedetomidine. *Middle East J Anaesthesiol*. 2006 Oct;18(6):1043-58.
32. Aksu R, Akin A, Biçer C, Esmaoğlu A, Tosun Z, Boyaci A. Comparison of the effects of dexmedetomidine versus fentanyl on airway reflexes and hemodynamic responses to tracheal extubation during rhinoplasty: A double-blind, randomized, controlled study. *Current therapeutic research*. 2009 Jun 30;70(3):209-20
33. Bindu B, Pasupuleti S, Gowd UP, Gorre V, Murthy RR, Laxmi MB. A double blind randomized controlled trial to study the effect of on haemodynamic and recovery responses during tracheal extubation. *Journal of Anaesthesiology Clinical Pharmacology*. 2013 Apr;29(2):162-7
34. Sağiroğlu AE, Celik M, Orhon Z, Yüzer S, Sen B. Different doses of dexmedetomidine on controlling haemodynamic responses to tracheal intubation. *Internet J Anesthesiol*. 2010;27:2.
35. Turan G, Ozgultekin A, Turan C, Dincer E, Yuksel G. Advantageous effects of dexmedetomidine on haemodynamic and recovery responses during extubation for intracranial surgery. *Eur J Anaesthesiol*. 2008 Oct; 25(10) :816-20. doi: 10.1017/S0265021508004201. Epub 2008 Apr 10.
36. Ramsay MA, Huddleston P, Hamman B, Tai S, Matter G. The patient state index correlates well with the Ramsay sedation score in ICU patients. *Anesthesiology*. 2004;101(A338):A338.
37. Miller KA, Harkin CP, Bailey PL. Postoperative tracheal extubation. *Anesth Analg*. 1995 Jan;80(1):149-72.
38. Mikawa K, Nishina K, Maekawa N, Obara H. Attenuation of cardiovascular responses to tracheal extubation: verapamil versus diltiazem. *Anesthesia & Analgesia*. 1996 Jun 1;82(6):1205-10.
39. Dodds TM, Stone JG, Coromilas J, Weinberger M, Levy DG. Prophylactic nitroglycerin infusion during noncardiac surgery does not reduce perioperative ischemia. *Anesth Analg*. 1993 Apr;76(4):705-13.
40. Jin F, Chung F. Minimizing perioperative adverse events in the elderly. *Br J Anaesth*. 2001 Oct;87(4):608-24.
41. Liu C, Zhang Y, She S, Xu L, Ruan X. A randomised controlled trial of dexmedetomidine for suspension laryngoscopy. *Anaesthesia*. 2013 Jan;68(1):60-6. doi: 10.1111/j.1365-2044.2012.07331.x. Epub 2012 Oct 29.
42. Guler G, Akin A, Tosun Z, Ors S, Esmoğlu A, Boyaci A. Single-dose dexmedetomidine reduces agitation and provides smooth extubation after pediatric adenotonsillectomy. *Pediatric Anesthesia*. 2005 Sep 1;15(9):762-6.
43. Talke P, Chen R, Thomas B, Aggarwall A, Gottlieb A, Thorborg P, Heard S, Cheung A, Son SL, Kallio A. The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery. *Anesth Analg*. 2000 Apr;90(4):834-9.
44. Ibacache ME, Muñoz HR, Brandes V, Morales AL. Single-dose dexmedetomidine reduces agitation after sevoflurane anesthesia in children. *Anesth Analg*. 2004 Jan;98(1):60-3, table of contents.
45. Kim YS, Kim YI, Seo KH, Kang HR. Optimal dose of prophylactic dexmedetomidine for preventing postoperative shivering. *Int J Med Sci*. 2013 Aug 13;10(10):1327-32. doi: 10.7150/ijms.6531. eCollection 2013.
46. Kim SY, Kim JM, Lee JH, Song BM, Koo BN. Efficacy of intraoperative dexmedetomidine infusion on

emergence agitation and quality of recovery after nasal surgery. *British journal of anaesthesia*. 2013 Aug 1;111(2):222-8.

47. Ramsay MA. Bariatric surgery: the role of dexmedetomidine. *Seminars in Anesthesia, Perioperative Medicine and Pain*. 2006 Jun 30;25(2):51-56.

48. Karaaslan K, Yilmaz F, Gulcu N, Colak C, Sereflican M, Kocoglu H. Comparison of dexmedetomidine and midazolam for monitored anesthesia care combined with tramadol via patient-controlled analgesia in endoscopic nasal surgery: A prospective, randomized, double-blind, clinical study. *Curr Ther Res Clin Exp*. 2007 Mar;68(2):69-81. doi: 10.1016/j.curtheres.2007.04.001.

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