



Attenuation of the Airway and Cardiovascular Responses to Extubation in Chronic Smokers by Prior Treatment with Dexmedetomidine, Fentanyl, and their Combination

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Abstract

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BACKGROUND: Respiratory complications and hemodynamic changes during and after extubation are more common than during tracheal intubation and induction of anesthesia.

AIM: The objective of this study was to compare the efficacy of prior treatment with dexmedetomidine, fentanyl, and their combination on the attenuation of the airway and cardiovascular responses to extubation.

METHODS: The subjects were adult chronic male smokers, representing the population in which secondary response to extubation is most common. A randomized double-blinded comparative trial was conducted on 66 patients who were 20–60 years of age, chronic male smokers, scheduled for elective surgeries, and divided into three equal groups according to given drug 20 min before the end of surgery. Group A (n = 22) received 1 µg·kg⁻¹ dexmedetomidine, Group B (n = 22) received fentanyl 1 µg·kg⁻¹, and Group C (n = 22) received a mixture of the previously used drugs in the same doses. Time to and quality of extubation, airway and hemodynamic responses, and post-operative agitation and sedation were recorded.

RESULTS: Hemodynamic responses and quality of extubation were better in both Groups A and C than patients in Group B at the expense of increasing time to extubation, post-extubation sedation, and delayed recovery in Group C.

CONCLUSION: Single-dose dexmedetomidine 1 µg·kg⁻¹ given 15 min before extubation in chronic cigarette smokers provided better attenuation of the airway and cardiovascular responses to extubation and suctioning with better recovery profile when compared to fentanyl 1 µg·kg⁻¹ and dexmedetomidine mixed with fentanyl in the same previous doses.

Introduction

Tracheal extubation is an essential procedure in anesthesia. While safely performed in a large proportion of cases, it can present significant challenges and complications when compared with intubation. This compares with the greater risk of aviation accidents during landing than during takeoff [1]. Complications associated with extubation can be severe, resulting in major morbidity and mortality [2].

Many smokers have hyperactive airway [3] and are prone to severe bronchospasm and desaturation during airway manipulation. The adrenergic receptors, particularly in the larynx, trachea, and bronchi [4], are stimulated by mechanical and chemical factors during extubation producing cardiovascular and respiratory reflex responses [5]. The plasma concentrations of noradrenaline and adrenaline will increase in chronic smokers causing tachycardia and hypertension which may result in complications such as cardiac failure, pulmonary edema, and cerebrovascular hemorrhage [4], [6].

Minimizing coughing on emergence should be emphasized, especially in particular surgeries to avoid complications, for example, abdominal surgeries (hematoma

formation and suture disruption), thyroidectomy (surgical bleeding), carotid endarterectomy (neck hematoma), and intracranial surgery (intracerebral hemorrhage) [7]. Special techniques and pharmacological methods may help to decrease airway reflexes and hemodynamic responses during extubation. Drugs that have been recommended for the control of these airway and hemodynamic events including opioids, lignocaine, beta-blockers, calcium channel blockers, and alpha-2 agonists [7].

The objective of this randomized double-blinded comparative study was to compare the effects of dexmedetomidine, fentanyl, and their combination on the attenuation of airway reflexes and hemodynamic responses to tracheal extubation in adults, chronic male cigarette smoking patients scheduled for elective surgeries (of average 2–3 h duration).

Materials and Methods

After approval from Ethics Committee at the National Cancer Institute, Cairo University, and obtaining written informed consent from patients, this

randomized double-blinded comparative trial was conducted on 66 patients who were 20–60 years of age, chronic male smokers, and scheduled for elective abdominal surgeries.

Inclusion criteria

The following criteria were included in the study:

- Chronic cigarette smokers (patients have smoked for 2 years at least and minimum consumption of 10 cigarettes/day) [8].
- American Society of Anesthesiologists (ASA) II.
- Body mass index of ≤ 30 kg/m².

Exclusion criteria

- 1- The following criteria were excluded from the study: History of opioid, sedative drugs, or medications affecting heart rate (HR) or blood pressure.
- 2- Morbid obesity.
- 3- Current upper respiratory infection
- 4- Hypovolemia
- 5- IHD
- 6- History of sleep apnea or expected difficult Intubation.
- 7- Emergency procedures.
- 8- Hepatic or renal impairment.
- 9- Drug allergy to dexmedetomidine or fentanyl.

Sample size estimation

Based on a previous study by Gosai *et al.* (2015) [8], and a large effect size of approximately 0.4 is expected. A total sample size of 66 (22 per group) will be sufficient to detect an effect size of 0.4, a power of 80%, and a significance level of 5%. The sample size was calculated using the G*Power program (University of Düsseldorf, Düsseldorf, Germany) [9].

Eligible patients using the sealed envelope technique were divided randomly into three different groups (22 subjects each) receiving the study drug over 15 min:

- Group (A): Will receive dexmedetomidine 1 ug. kg⁻¹ in 100 ml normal saline (NS) intravenous (IV)
- Group (B): Will receive fentanyl citrate 1 ug. kg⁻¹ in 100 ml NS IV
- Group (C): Will receive both dexmedetomidine 1 ug. kg⁻¹ mixed with fentanyl 1 ug. kg⁻¹ in 100 ml NS IV.

A pre-anesthetic checkup was conducted and an in-depth history and complete physical examination were recorded. Routine investigations such as complete blood picture, blood grouping/typing, blood urea, and

serum creatinine were done. Patients fulfilling inclusion criteria were informed about the procedure and its possible complications. Finally, a written consent was taken. Premedication with midazolam 0.05 mg.kg⁻¹, ondansetron 4 mg and ranitidine 50 mg IV followed by preoxygenation with 100% oxygen for 3 min was done. Induction with routine anesthetic technique was used using propofol 2 mg.kg⁻¹, fentanyl 2 ug.kg⁻¹, and atracurium 0.5 mg.kg⁻¹ followed by intubation with an appropriate endotracheal tube (ETT). Anesthesia was maintained by oxygen/air mixture in a ratio of 40:60 and sevoflurane 2%, atracurium 0.125 mg at intervals with adequate volume replacement. Standard monitoring with electrocardiography, pulse oximetry (SpO₂), non-invasive BP, and capnograph was done.

About 15 min before the estimated end of surgery (or at the start of the closure of skin incision), the inhalation agent (sevoflurane) was stopped and the patient was kept on 100% oxygen. Ketorolac 30 mg slowly IV and paracetamol 1000 mg IV infusion were given and the patients in each group received the specified solution IV over 15 min.

Patients in Group A received dexmedetomidine 1 ug. kg⁻¹ IV in 100 ml NS over 15 min, patients in Group B received Fentanyl 1 ug. kg⁻¹ (IV) in 100 ml NS over 15 min, while patients in Group C received both dexmedetomidine 1 ug. kg⁻¹ mixed with fentanyl 1 ug. kg⁻¹ in 100 ml NS over 15 min.

When patients' spontaneous respiration was considered sufficient, being hemodynamically stable and ready to obey simple commands; the residual neuromuscular block was antagonized with neostigmine 0.05 mg. kg⁻¹ and atropine 0.02 mg. kg⁻¹. Oropharyngeal secretions were aspirated. The ETT was removed after the standards of extubation were fulfilled.

The anesthesiologist performing the extubation was blinded to the study drugs. HR, systolic BP, diastolic BP, and oxygen saturation were recorded at the beginning of bolus drug injection and thereafter at 1, 3, 5, 10, and 15 min, also at the time of extubation and thereafter at 1, 3, and 5 min after extubation followed by every 5 min for ½ h. Duration of anesthesia and surgery was noted.

Groups were monitored and compared for:

Primary goals

- Time to extubation (from inhaled anesthetic stop to ETT removal) was recorded.
- Quality of extubation was evaluated immediately after extubation, employing a 5-point rating scale (Quality of Extubation Score) [10]:
 1. No coughing
 2. Smooth extubation, minimal coughing (1 or 2 times)
 3. Moderate coughing (3 or 4 times)

4. Severe coughing (5–10 times) and straining
5. Poor extubation, very uncomfortable (laryngospasm and coughing >10 times).

Secondary goals

- Hemodynamic responses (HR, systolic blood pressure [SBP], and diastolic blood pressure [DBP]).
- Incidence of complications in the form of laryngospasm, bronchospasm, desaturation, and bradycardia was defined as HR <60/min and treated with a rescue dose of injection atropine 0.6 mg intravenously, tachycardia (being 20% increase from baseline), hypertension (as either 20% increase from baseline or SBP >180 mmHg), or hypotension (as 20% decrease from baseline or SBP <80 mmHg).
- Post-operative agitation and sedation were evaluated on a 10 points scale (Richmond Agitation Sedation Scale [RASS] scale) [11]: (+4) Combative, (+3) very agitated, (+2) agitated, (+1) restless, (0) alert and calm, (-1) drowsy, (-2) light sedation, (-3) moderate sedation, (-4) deep sedation, and (-5) unarousable.

Statistical analysis

Statistical analysis was done using IBM® SPSS® Statistics version 23 (IBM® Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between the three groups was done using ANOVA test, then *post hoc* "Scheffe test" was used for pairwise comparison. Two-way ANOVA was invalid due to interaction, therefore, consecutive measures in each group were compared separately with ANOVA for repeated measures. This was followed by the appropriate *post hoc* test, with correction of the p-values. $p < 0.05$ was considered statistically significant.

Results

The mean age of the study patients was 35.53 ± 15.83 years, and there was no statistically significant difference in demographic data, ASA, or duration of surgery of the study group.

Primary goals

The time to extubation was significantly prolonged in the combined group (Group C). The quality of extubation score was significantly higher in the Fent group (Group-B).

Secondary goals

We had chosen six readings; baseline and 15 min after bolus injection, then immediately after extubation (at 0 min), and 1, 3, and 5 min after extubation.

- Changes in HR
- Changes in SBP
- Changes in DBP
- Incidence of complications.

Hypotension

Hypotension was significantly (Table 1) more frequent in the combined group.

Table 1: Incidence of hypotension in the three study groups

Study groups	Group			Total
	Dex group	Fentanyl group	Combined group	
Hypotension				
Yes				
Count	5	0	9	14
% within group	22.7%	0.0%	40.9%	21.2%
No				
Count	17	22	13	52
% within group	77.3%	100.0%	59.1%	78.8%
Total				
Count	22	22	22	66
% within group	100.0%	100.0%	100.0%	100.0%
Chi-square tests				
Value				p-value
Fisher's exact test	12.188			0.002

Bradycardia

Bradycardia was significantly more frequent in the combined group (Table 2).

Table 2: Incidence of bradycardia in the three study groups

Study groups	Group			Total
	Dex group	Fentanyl group	Combined group	
Bradycardia				
Yes				
Count	2	1	15	18
% within group	9.1%	4.5%	68.2%	27.3%
No				
Count	20	21	7	48
% within group	90.9%	95.5%	31.8%	72.7%
Total				
Count	22	22	22	66
% within group	100.0%	100.0%	100.0%	100.0%
Chi-square tests				
Value				p-value
Pearson Chi-square	27.958			0.000

Hypertension

Hypertension was only monitored in two cases of the Fent group (Group B) (Table 3).

Table 3: Incidence of hypertension in the three study groups

Study groups	Group			Total
	Dex group	Fentanyl group	Combined group	
Hypertension				
Yes				
Count	0	2	0	2
% within group	0.0%	9.1%	0.0%	3.0%
No				
Count	22	20	22	64
% within group	100.0%	90.9%	100.0%	97.0%
Total				
Count	22	22	22	66
% within group	100.0%	100.0%	100.0%	100.0%
Chi-square tests				
	Value		p-value	
Fisher's exact test	2.752		0.323	

Tachycardia

Tachycardia was significantly more frequent in the fentanyl group (Table 4).

Table 4: Incidence of tachycardia in the three study groups

Study groups	Group			Total
	Dex group	Fentanyl group	Combined group	
Tachycardia				
Yes				
Count	0	11	0	11
% within group	0.0%	50.0%	0.0%	16.7%
No				
Count	22	11	22	55
% within group	100.0%	50.0%	100.0%	83.3%
Total				
Count	22	22	22	66
% within group	100.0%	100.0%	100.0%	100.0%
Chi-square tests				
	Value		p-value	
Fisher's exact test	23.661		0.000	

RASS scale

RASS scale was monitored, showing the best recovery in the Fent group (Group B) (Table 5).

Table 5: Comparison between groups according to RASS scale

Study groups	RASS scale		
	Median	Minimum	Maximum
Group			
Dex group	-2.0	-2.0	-1.0
Fentanyl group	0.0	-1.0	0.0
Combined group	-4.0	-4.0	-3.0

Discussion

In this study, patients were comparable regarding demographic data, ASA, and duration of surgery (Table 6). HR showed significant differences between the three study groups. Significant decrease following injection of the study drug was obvious in Group C (Dex-Fent) (Figure 1), which was maintained even during extubation and suctioning processes till 30 min following extubation.

Table 6: Comparison between groups according to age and duration of surgery

	Group						F	p-value
	Dex group		Fentanyl group		Combined group			
	Mean	SD	Mean	SD	Mean	SD		
Age	35.5	13.6	34.0	14.8	37.1	14.7	0.262	0.770
Duration	2.5	0.4	2.5	0.5	2.6	0.4	0.255	0.776

Using: F-One-Way analysis of variance; Chi-square test, p > 0.05 NS.

At the critical time of extubation, an increase of HR was the foremost in Group B (Fent group) and the least in Group C (Dex-Fent). Amutharani *et al.* (2019) [10] when compared dexmedetomidine 0.5 $\mu\text{g.kg}^{-1}$ infusion administered 10 min before tracheal extubation to fentanyl 1 $\mu\text{g.kg}^{-1}$ infusion also located that dexmedetomidine group had a statistically significant lesser increase in HR than the fentanyl group during extubation and up to 100 min after extubation. On the contrary, Shrirang *et al.* (2015) [12] noticed the occurrence of tachycardia in 7% of the study group received dexmedetomidine 0.5 $\mu\text{g.kg}^{-1}$ before extubation over 10 min, which was not the case in our study. Tachycardia (20% increase from baseline) was only significant in Group B cases following extubation.

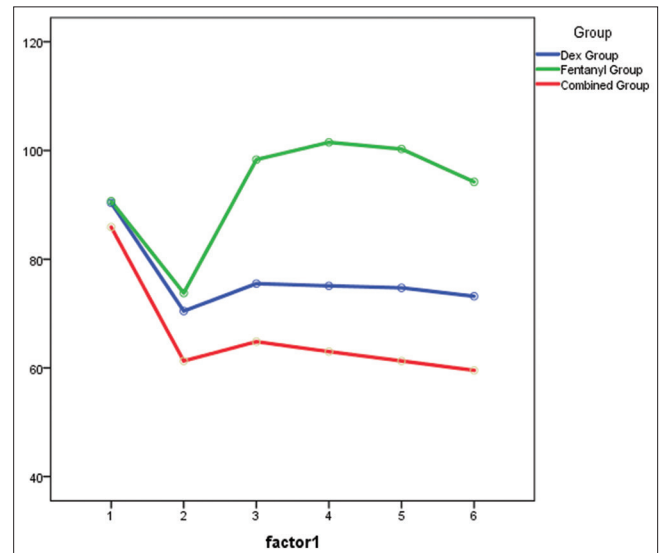


Figure 1: It showed what happened at the critical time #3: Rise of heart rate more with fentanyl and least with the combined group

SBP (Figure 2) and DBP (Figure 3) showed an initial decrease within the three study groups following injection of the study drug. Following extubation, both SBP and DBP showed the highest readings within Group B, and it took 5 min after extubation to start to decrease again. While in both Groups A and C, SBP was maintained on the rock bottom side. Amutharani *et al.* (2019) [10] mentioned also that dexmedetomidine had the more significant control of SBP than the fentanyl group during extubation and up to 70 min after extubation and a lesser rise in DBP and mean blood pressure compared to the fentanyl group from 5 min before extubation to 130 min after extubation. Rani *et al.* (2016) [13] recorded a statistically significant drop in blood pressure at 5 min after test drug administration in both the groups; those receiving fentanyl 1 $\mu\text{g/kg}$ compared with the dexmedetomidine 0.75 $\mu\text{g.kg}^{-1}$, given 15 min before the end of surgery as an infusion over 5 min, which we think that it was related to the rate of infusion. On the other hand, Üstün *et al.* (2006) [14] mentioned the incidence of a biphasic arterial blood pressure response; a short-lived increase in blood pressure and reflex decrease in pulse after injection of dexmedetomidine 4 $\mu\text{g.kg}^{-1}$ during intravenous conscious sedation in the third molar surgery which we guess that it may be related to the given higher dose of dexmedetomidine than in our study.

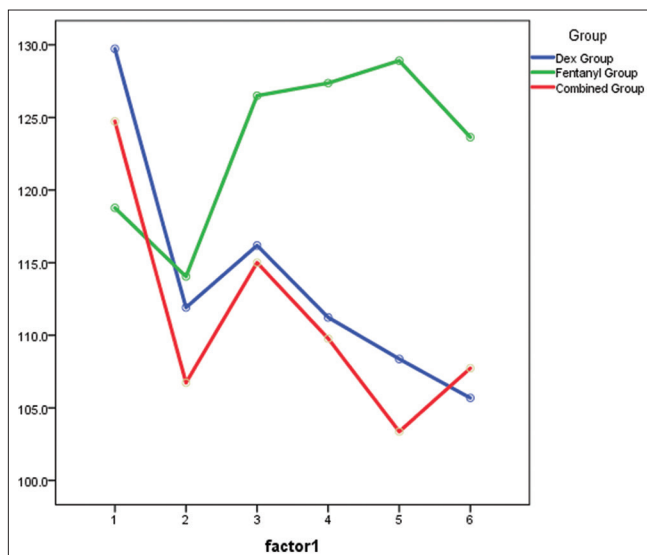


Figure 2: It showed that systolic blood pressure decreased 1 min after extubation in Dex and combined groups, but in fentanyl, it took 5 min to decrease

The time to extubation was significantly prolonged only within Group C in comparison with the opposite two groups, which may be due to the added effect of fentanyl and dexmedetomidine (Table 7). Aksu *et al.* (2009) [15] also found that dexmedetomidine 0.5 $\mu\text{g.kg}^{-1}$ IV, administered before extubation, was more effective in attenuating airway reflex responses to tracheal extubation and maintaining hemodynamic stability without prolonging recovery compared with fentanyl 1 $\mu\text{g.kg}^{-1}$ IV in patients undergoing rhinoplasty. Fan *et al.* (2015) [6] compared remifentanyl 0.03 $\mu\text{g.kg}^{-1}$ min, dexmedetomidine 0.5 $\mu\text{g.kg}^{-1}$, and dexmedetomidine 0.7 $\mu\text{g.kg}^{-1}$ infusion for 10 min at end of otologic surgery and stated that the higher dose of dexmedetomidine (0.7 $\mu\text{g/kg}$) was associated with a higher percentage of patients with smooth extubation and did not exhibit

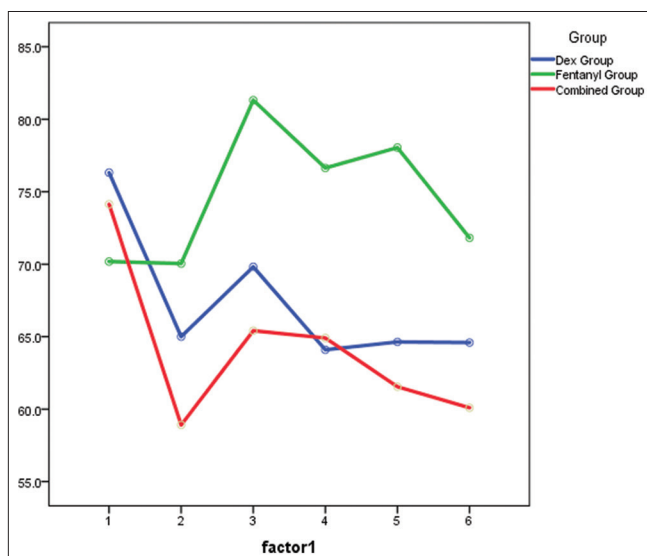


Figure 3: It showed changes in diastolic blood pressure in the three groups. The changes were of a similar pattern but smoother in the combined group

a prolonged time to wake when it was compared to the other two groups. While Lee *et al.* (2015) [16] claimed that the addition of a single dose of dexmedetomidine (0.5 $\mu\text{g/kg}$) to a low-dose remifentanyl infusion (TCI 1 ng.ml^{-1}) resulted in delayed the time to awakening and extubation. This may be due to this combination of both drugs.

Table 7: Comparison between groups according to time and quality of extubation

	Group						Between groups		
	Dex group		Fentanyl group		Combined group		ANOVA	Chi-square	p-value
	Mean	SD	Mean	SD	Mean	SD			
Time to extub.	18.0	2.0	15.5	0.9	21.1	2.4	37.308		< 0.001
Quality of extub.	2.3	0.5	3.5	0.5	2.4	0.5		38.753	< 0.001

Using: F-One-Way analysis of variance; **p < 0.001 HS. Using: Chi-square test; *p < 0.05 S.

A (Table 7) statistically significant difference between the three groups was present regarding the quality of extubation with no incidence of laryngospasm or bronchospasm within the three sample groups. The most favorable profile was seen within Group A having smooth extubation with minimal cough followed by Group C, with the remainder of cases within the previous two groups were experiencing moderate cough up to 3- or 4-fold following extubation improved after proper suctioning and were not related to any desaturation, laryngospasm, or bronchospasm. On the opposite hand, within Group B; quite half of the sample size developed a severe cough and strain up to 6 times, while the rest showed moderate cough up to 3 or 4 times. The quality of extubation score showed the most favorable profile within Group A. Aksu *et al.* (2009) [15] and Rani *et al.* (2016) [13] found the same; that is, extubation quality was found to be superior in dexmedetomidine group with patients arousable and tolerating suctioning and extubation compared with fentanyl group. Furthermore, Aksu *et al.* (2009) [15] mentioned that the fentanyl group had a prevalence of cough (70%), 20% of which was severe. The lower prevalence of cough (15%) found with dexmedetomidine compared with fentanyl suggests that dexmedetomidine

was more effective for improving the quality of extubation. Tung *et al.* (2020)[17] did a systematic review and meta-analysis of dexmedetomidine, remifentanyl, fentanyl, lidocaine IV, intracuff lidocaine, and lidocaine through tracheal or topical route, demonstrated that in pairwise comparisons, all study medications were equivalent in reducing moderate and severe emergence coughing incidence, and were better than placebo or nothing.

Dexmedetomidine had the very best cumulative rank (81.0%) for decreasing the incidence of moderate to severe peri-extubation coughing, followed by remifentanyl (67.2%), fentanyl (66.2%), lidocaine intracuff (59.5%), lidocaine TT/topical (59.2%), and lidocaine IV (52.4%) therein order.

The level of sedation showed the most favorable picture in Group B, followed by Group A (Table 7). On the opposite hand, quite half Group C patients experienced deep sedation with the remainder of the sample size patients in moderate sedation post-extubation.

Conclusion

Single-dose dexmedetomidine 1 ug.kg^{-1} given 15 min before extubation in chronic cigarette smoker undergoing elective surgery provided a better attenuation of the airway and cardiovascular responses to extubation and suctioning, and a better recovery profile when compared to fentanyl 1 ug.kg^{-1} along with improving quality of extubation. Dexmedetomidine 1 ug.kg^{-1} when mixed with fentanyl 1 ug.kg^{-1} also provided tight control on hemodynamics and airway responses to extubation comparable to the dexmedetomidine alone group but at the expense of prolonged time to extubation, post-operative sedation, and delayed recovery.

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