Original Article

Evaluation of different doses of dexmedetomidine alone versus the combination of dexmedetomidine and fentanyl in sedation during awake fiberoptic intubation in oral cancer surgery patients: A prospective, randomized, double-blind clinical trial

ABSTRACT

Background: Awake fiberoptic intubation (AFOI) is one of the principal techniques in the management of difficult airway in oral cancer surgery. We hypothesized that the addition of a small dose of fentanyl could improve the sedative criteria of dexmedetomidine during AFOI technique, without the need to increase the dose of dexmedetomidine which may be associated with airway compromise.

Patients and Methods: One hundred and fifty American Society of Anesthesiologists physical status 1 and 2 patients planned for AFOI for oral cancer surgery patients were allocated into three groups (fifty patients each). Group D1: Received an infusion of 1 μcg/kg dexmedetomidine diluted in 50 ml saline over 20 min. Group D2: Received an infusion of 2 μcg/kg dexmedetomidine diluted in 50 ml saline over 20 min. Group DF: Received an infusion of 1 μcg/kg dexmedetomidine added to 1 μcg/kg fentanyl diluted in 50 ml saline over 20 min. AFOI was done by topical anesthesia and with the same technique in all patients. All patients were assessed for: airway obstruction, intubation scores (vocal cord movement, coughing, and limb movement), fiberoptic intubation scores, and hemodynamic variables. Any episode of bradycardia or hypoxia was recorded and managed.

Results: Group D2 showed more incidence of airway obstruction than the other two groups. Limb movement scores were more in Group D1 compared to the other two groups. All groups were comparable as regard fiberoptic intubation scores, coughing, and vocal cord opening scores.

Conclusion: Adding a low dose of fentanyl (1 μcg/kg) to a low dose of dexmedetomidine can prevent the risk of airway obstruction associated with increasing the dose of dexmedetomidine while achieving the same favorable intubation scores.

Key words: Airway; awake fiberoptic; dexmedetomidine; fentanyl

Introduction

Airway obstruction can occur during difficult airway management in oral cancer patients, especially in "cannot intubate cannot ventilate" conditions, and this situation may result in hypoxia and consequent serious complications. Awake fiberoptic intubation (AFOI) is one of the principal techniques guaranteed by the American Society of

Access this article online	
Website: www.saudija.org	Quick Response Code
DOI: 10.4103/1658-354X.203013	

How to cite this article: Hassan ME, Mahran E. Evaluation of different doses of dexmedetomidine alone versus the combination of dexmedetomidine and fentanyl in sedation during awake fiberoptic intubation in oral cancer surgery patients: A prospective, randomized, double-blind clinical trial. Saudi J Anaesth 2017;11:196-202.

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Anesthesiologists (ASA) guidelines to manage these difficult situations.[1] Therefore, the selection of an ideal agent that can efficiently sedate the patient without compromising the patency of the airway is very important for AFOI procedures done for oral cancer patients.[2]

Several sedative agents have been used successfully for conscious sedation during AFOI such as dexmedetomidine, fentanyl, remifentanil, propofol, ketamine, and benzodiazepines.[1-7]

Dexmedetomidine is a selective α_2 agonist with central action on presynaptic α_2 receptors, resulting in a negative feedback decreasing the availability of epinephrine and norepinephrine on postsynaptic α_1 receptors.[8] In addition, it has an antisialagogue action which is beneficial in AFOI.[9]

Opioids such as remifentanil, sufentanil, and fentanyl had been used in this procedure (AFOI) in previous clinical trials as they can blunt sympathetic response to intubation resulting in more hemodynamic stability and more comfort to the patient during intubation.[1,3,10,11]

Some authors successfully used dexmedetomidine as a single agent for sedation during AFOI,[3,4,12] and others combined it with other agents as a trial to improve its sedation criteria,[5,6] but the combination of fentanyl with dexmedetomidine was not used before.

To establish a better safe regimen of sedation while maintaining patency of airway, we assumed that the addition of a small dose of fentanyl (1 μcg/kg) can improve the sedative criteria of dexmedetomidine in the form of improving tolerance of the oral cancer patients to intubation during AFOI technique, without the need to increase the dose of dexmedetomidine which may be associated with airway compromise. We conducted this study to evaluate this assumption.

Patients and Methods

After obtaining approval from the Local Ethics Committee and written informed consent, 150 ASA physical status 1 and 2 patients were included in this study. Inclusion criteria were ages from 18 to 60 years old and surgeries dealing with oral cancer with a plan for awake nasal fiberoptic intubation as an airway management technique to deal with the difficult airway situation in these patients. This study was carried out at the National Cancer Institute– Cairo University.

Exclusion criteria were respiratory, hepatic, renal, neurological or psychiatric diseases, pregnancy, bradycardia (heart rate [HR] <60 beats/minute) or any type of A-V block demonstrated in electrocardiogram (ECG), uncontrolled hypertension, morbid obesity, bleeding disorder with contraindication for nasal intubation, known allergy to one of the study medications, and lack of cooperation or effective communication.

The awake fiberoptic technique was applied on all patients by the same single anesthesiologist who was unaware of the type of medication given to each patient. Observations were recorded by another anesthesiologist who was also unaware of the type of medication given to each patient.

After fasting for more than 6 h, all patients were premedicated 30 min before the procedure by metoclopramide 10 mg intravenous (i.v.), ranitidine 50 mg i.v., and atropine 0.3 mg i.v.

Randomization occurred before entry to the operating theater using a computer-generated random numbers concealed in sealed opaque envelopes assigning the patients into three groups (Group D1, Group D2, and Group DF).

After entry to operating theaters, routine multichannel monitoring devices were conducted to all patients where baseline hemodynamic variables as HR, systolic blood pressure, diastolic blood pressure, oxygen saturation, and ECG were recorded. Then, an i.v. line was established and administration of 500 cc lactated ringer infusion started.

In the operating theater, every patient received his medication as i.v. infusion for 20 min according to the assignment done before as follows: (1) Group D1: Received an infusion of 1 μcg/kg dexmedetomidine diluted in 50 ml saline. (2) Group D2: Received an infusion of 2 μcg/kg dexmedetomidine diluted in 50 ml saline. (3) Group DF: Received an infusion of 1 μcg/kg dexmedetomidine added to 1 μcg/kg fentanyl diluted in 50 ml saline.

Oxymetazoline nasal drops were applied to both nostrils as a vasoconstrictor to decrease the risk of bleeding. A nasal pack soaked with lidocaine 2% and adrenaline 1/200,000 was placed in the nostril selected for the fiberoptic intubation which was the nostril that was less resistant to the nasal pack, while the other nostril received oxygen insufflation through a nasal cannula with oxygen flow 4 L/min. Lidocaine 2% nebulizer was given to all patients for at least 10–15 min.

Airway manipulation started 20 min after the administration of the study drugs. A lubricated spiral tube (7.0 mm diameter in males and 6.5 mm diameter in females) was loaded in the fiberoptic scope after softening of the tube by immersing it

in warm water. Airway manipulation started using the spray as you go technique to intensify the topical anesthesia. With visualization of the supraglottic region, 2 ml lidocaine 2% was given through the working channel of the scope, and the manipulation of the scope was performed until visualization of the vocal cords, where 4 ml lidocaine 2% was sprayed in both glottic and infraglottic regions. After that the device was passed through vocal cords, and then the tube was advanced over the scope up to 2–3 cm above the carina. After confirmation of the proper position of the tube by capnography and visualization of the carina by the scope, the cuff was inflated and the tube was secured in place. Then, general anesthesia was carried out by propofol 2 mg/kg, rocuronium 0.5 mg/kg, and fentanyl 1 μcg/kg, and mechanical ventilation was applied.

Atropine 0.5 mg i.v. was given during any recorded bradycardia episode and crystalloid infusion and ephedrine increments of 10 mg were planned to be given to treat any hypotensive episode throughout the procedure.

Oxygen insufflation through the oxygen port of the scope was planned to correct any episode of hypoxia (oxygen saturation <90%) occurring during the procedure. If this was not enough, temporary removal of the scope and bag mask ventilation with oxygen 100% took place.

Primary outcome measurements

(1) Airway obstruction score was evaluated using a 3-degree scale (1 = no airway obstruction, 2 = airway obstruction relieved by neck extension, and 3 = airway obstruction requiring jaw thrust). (2) Intubation score[12] was evaluated according to (i) vocal cord movement (1 = open, 2 = moving, 3 = closing, and 4 = closed). (ii) Coughing: (1 = none, 2 = slight, 3 = moderate, and 4 = severe). (iii) Limb movement: (1 = none, 2 = slight, 3 = moderate, and 4 = severe). (3) Fiberoptic intubation comfort score indicating patient tolerance; it was evaluated using a 5-point score (1 = no reaction, 2 = slight grimacing, 3 = heavy grimacing, 4 = verbal objection, and 5 = defensive movement of head and hands).

Secondary outcome measurements

(1) Hemodynamic variables as HR, systolic blood pressure, and diastolic blood pressure. This took place at three-time points:
   (i) Baseline: Before drug administration
   (ii) With the start of the airway manipulation technique (20 min after drug administration)
   (iii) Immediately after intubation. (2) Any episode of oxygen desaturation (<90%) or bradycardia (HR <60 beats/minute).

Sample size estimation

Provided that the primary outcome assessment will be the degree of airway obstruction and based on the previous study done by Tsai *et al*., who found that the incidence of airway obstruction with dexmedetomidine 1 μcg/kg was 0%,[4] and also based on the previous study done by Liu *et al*., who found that the incidence of airway obstruction with dexmedetomidine more than 1 μcg/kg was 22%,[3] the calculated sample size was 31 patients for each group to detect this expected difference (22%), with significance level (α) of 0.05 and power of the test (β) of 0.8. To increase the power of the study and to compensate for drop-outs, we increased the sample to be fifty patients per group.

Statistical methods

Statistical Package for Social Sciences (SPSS) for Windows, Version 22.0. Armonk, NY: IBM Corp. was used for data management and data analysis. Mean ± standard deviation described quantitative demographic and hemodynamic variables. Number and percentages described qualitative data (as airway obstruction scores, intubation scores, and fiberoptic intubation comfort scores) and Chi-square or Fisher's exact tested proportion independence. For comparing mean values of more than two independent groups, one-way analysis of variance (ANOVA) was used. Mixed model ANOVA with repeated measures was used to test the effect of time on blood pressure with group interaction. All pair-wise comparisons were Bonferroni adjusted. *P* value was always two tailed and significant at 0.05 level.

Results

All patients underwent a successful AFOI without significant difference between the three groups in regards to the demographic data (age, weight, height, and sex) [Tables 1 and 2].

In regards to hemodynamic parameters (systolic and diastolic blood pressure and HR), the present study revealed a significant decrease from baseline till the time of intubation

Table 1: Comparison of demographic data in the three study groups

	Mean±SD (groups)			
	D1	D2	DF	*P**
Age (years)	50.88±7.06	49.16±8.92	48.78±7.39	0.36
Height (cm)	164.38±6.23	166.06±4.53	165.18±4.54	0.27
Weight (kg)	79.98±10.01	79.56±8.82	79.32±7.16	0.93
BMI	29.59±3.24	28.86±2.99	29.13±3.03	0.49

Values are expressed in mean (SD). BMI: Body mass index; SD: Standard deviation; Group (D1): Dexmedetomidine low-dose group; Group (D2): Dexmedetomidine high-dose group; Group (DF): Combined dexmedetomidine low-dose and fentanyl low-dose group. **P* value is significant ≤0.05

(after administration of the study drugs) followed by a slight significant increase after intubation but still less than baseline. However, all groups were similar in hemodynamic values at all-time points with no interaction between them [Tables 3-5].

Increasing the dose of dexmedetomidine resulted in a significant increase in airway obstruction in group D2 (with $P = 0.01$). Four patients (8%) in group D2 suffered from airway obstruction that was relieved by jaw thrust, and six patients required only neck extension to relieve airway obstruction, while none of the patients required jaw thrust in the other two groups [Table 6].

Regarding the intubation scores, in Group D1, one patient showed closed vocal cords and three patients showed closing vocal cords, and these values were higher than that of both other groups D2 and DF, in which no patients showed closed vocal cords and only one patient showed closing vocal cords. Only two cases in group DF had severe cough, while four cases in Group D1 had severe cough during the study. However, these results regarding vocal cord movement and cough scores were statistically insignificant [Table 6].

Adding a small dose of fentanyl to low-dose dexmedetomidine in Group DF resulted in more patients with no limb movement throughout the procedure (13 patients) compared with

Table 2: Sex comparison between the three groups

Sex	Groups						*P**
	D1		D2		DF		
	Count	Percentage	Count	Percentage	Count	Percentage	
Male	26	52.0	29	58.0	27	54.0	0.83
Female	24	48.0	21	42.0	23	46.0	
Total	50	100.0	50	100.0	50	100.0	

**P* value is significant≤0.05. Group (D1): Dexmedetomidine low-dose group; Group (D2): Dexmedetomidine high-dose group; Group (DF): Combined dexmedetomidine low-dose and fentanyl low-dose group

Table 3: Comparison of systolic blood pressure over intubation time and among the three study groups

Groups	Mean±SD			*P* value for time effect*
	SBP baseline	SBP start of intubation	SBP immediate after intubation	
D1	$133.10^{a}\pm18.38$	$111.30^{c}\pm14.67$	$118.60^{b}\pm16.20$	<0.001
D2	$131.40^{a}\pm14.71$	$107.30^{c}\pm11.12$	$116.40^{b}\pm11.91$	
DF	$132.40^{a}\pm15.03$	$109.00^{c}\pm10.97$	$116.50^{b}\pm11.48$	
P value for group interaction		0.23		

**P* value is significant ≤0.05, times sharing same letter are not different. Group (D1): Dexmedetomidine low-dose group; Group (D2): Dexmedetomidine high-dose group; Group (DF): Combined dexmedetomidine low-dose and fentanyl low-dose group; SD: Standard deviation; SBP: Systolic blood pressure

Table 4: Comparison of diastolic blood pressure over intubation time and among the three study groups

Groups	Mean±SD			*P* value for time effect*
	DBP baseline	DBP start of intubation	DBP immediate after intubation	
D1	$84.80^{a}\pm9.69$	$70.30^{c}\pm10.57$	$77.20^{b}\pm9.64$	<0.001
D2	$84.10^{a}\pm8.37$	$71.80^{c}\pm7.81$	$76.80^{b}\pm7.61$	
DF	$82.50^{a}\pm10.06$	$72.80^{c}\pm9.75$	$76.40^{b}\pm9.48$	
P value for group interaction		0.07		

**P* value is significant ≤0.05, times sharing same letter are not different. Group (D1): Dexmedetomidine low-dose group; Group (D2): Dexmedetomidine high-dose group; Group (DF): Combined dexmedetomidine low-dose and fentanyl low-dose group; DBP: Diastolic blood pressure; SD: Standard deviation

Table 5: Comparison of heart rate over intubation time and among the three study groups

Groups	Mean±SD			*P* value for time effect*
	DBP baseline	DBP start of intubation	DBP immediate after intubation	
D1	$88.10^{a}\pm8.38$	$72.20^{c}\pm6.79$	$78.70^{b}\pm8.19$	<0.001
D2	$88.30^{a}\pm9.01$	$70.00^{c}\pm6.78$	$77.00^{b}\pm7.28$	
DF	$86.00^{a}\pm10.97$	$68.10^{c}\pm8.07$	$74.30^{b}\pm8.69$	
P value for group interaction		0.16		

**P* value is significant ≤0.05, times sharing same letter are not different. Group (D1): Dexmedetomidine low-dose group; Group (D2): dexmedetomidine high-dose group; Group (DF): Combined dexmedetomidine low-dose and fentanyl low-dose group; HR: Heart rate; DBP: Diastolic blood pressure; SD: Standard deviation

Table 6: Comparison of different scores: airway obstruction, intubation scores, and fiberoptic intubation comfort scores

	Groups						*p*
	D1		D2		DF		
	n	Percentage	*n*	Percentage	*n*	Percentage	
Degrees of airway obstruction							
No	48/50	96	40/50	80	47/50	94	0.01*
Relieved by neck extension	2/50	4	6/50	12	3/50	6	
Requiring jaw thrust	0/50	0	4/50	8	0/50	0	
Degree of vocal cords movement							
Open	28/50	56	34/50	68	33/50	66	0.69
Moving	18/50	36	15/50	30	16/50	32	
Closing	3/50	6	1/50	2	1/50	2	
Closed	1/50	2	0/50	0	0/50	0	
Degree of cough							
None	16/50	32	19/50	38	18/50	36	0.75
Slight	25/50	50	28/50	56	27/50	54	
Moderate	5/50	10	2/50	4	3/50	6	
Severe	4/50	8	1/50	2	2/50	4	
Degree of limb movement							
None	8/50	16	21/50	42	13/50	26	<0.001
Slight	16/50	32	21/50	42	23/50	46	
Moderate	22/50	44	8/50	16	14/50	28	
Severe	4/50	8	0/50	0	0/50	0	
Degree of intubation comfort							
No reaction	4/50	8	12/50	24	10/50	20	0.27
Slight grimacing	25/50	50	28/50	56	27/50	54	
Heavy grimacing	11/50	22	5/50	10	6/50	12	
Verbal objection	5/50	10	4/50	8	4/50	8	
Defensive movement of head and hands	5/50	10	1/50	2	3/50	6	

*P value is significant ≤0.05. Group (D1): Dexmedetomidine low-dose group; Group (D2): Dexmedetomidine high-dose group; Group (DF): Combined dexmedetomidine low-dose and fentanyl low-dose group

low-dose dexmedetomidine in Group D1 which resulted in only eight cases with no limb movement. Severe limb movement was observed with four patients in Group D1 with lower dose of dexmedetomidine, and moderate limb movement was observed with 22 patients of this group, and this finding was different from that of the two other groups, whose patients were compared in regards of the degree of limb movement during intubation [Table 6]. These values were statistically significant with $P < 0.001$.

With respect to patient tolerance to intubation, ten patients in Group DF and 12 patients in Group D2 showed no reaction to intubation, while only four patients in Group D1 showed no reaction to intubation. The number of patients who showed the defensive movement of the head and neck during intubation was five patients in Group D1 which was higher than other two groups (one patient and three patients in Groups D2 and DF, respectively). However, all these changes shown in our study were statistically insignificant [Table 6].

There were three cases of bradycardia (HR <60) in this study in Groups D2 and DF (two cases in Group D2 and one case in Group DF), while none in group D1. No events of oxygen desaturation (SaO_2<90%) were reported in this study.

Discussion

This study revealed that the addition of a small dose of fentanyl (1 μcg/kg) to a small dose of dexmedetomidine (1 μcg/kg) resulted in improvement of limb movement scores during intubation at an extent similar to a high dose of dexmedetomidine (2 μcg/kg). Increasing the dose of dexmedetomidine (2 μcg/kg) was associated with increased risk of airway obstruction more than a small dose of dexmedetomidine or the combination of small doses of both fentanyl and dexmedetomidine.

The aim of ideal sedation during AFOI is to achieve smooth patient tolerance of the technique through blunting of airway reflexes and attenuating the hemodynamic sympathetic response to intubation, while simultaneously achieving adequate cooperative and spontaneous breathing through a safe patent airway.[1]

Dexmedetomidine was reported by Abdelmalek *et al*. in 2007 to be used successfully for sedation during a series of AFOI in patients with a difficult airway,[9] and subsequently, dexmedetomidine has been proved to be efficient in sedation during AFOI in multiple clinical trials.[1,4,6,7,11]

Inhibition of sympathetic pathway involved in α_1 receptors done by dexmedetomidine explains its action of decreasing HR and blood pressure. This action is very useful in attenuating the hemodynamic sympathetic response done in AFOI specially after intubation.[13,14] Inhibition of sympathetic supply of upper airways by dexmedetomidine results in blunting of airway reflexes, with more comfort to patients during intubation, and this is very helpful in allowing smooth intubation and easy ensuring of endotracheal tube position[2] and this explains the favorable outcomes during intubation.

Increase of norepinephrine production in response to anxiety and stress is done mainly in locus ceruleus which is a pontine nucleus. Locus ceruleus is the principal site of action of α_2 agonists, unlike other gamma-aminobutyric acid mimetic drugs that act mainly on cerebral cortex. This explains the unique advantage of dexmedetomidine in efficient sedation while the patient is still arousable and cooperative.[15]

The ideal dose of dexmedetomidine should be high enough to blunt airway reflexes and achieve good sedation but not to the extent that results in airway relaxation and collapse which are very critical in such oral cancer patients. This optimum dose is still uncertain.[3]

In a clinical trial to reach to this ideal dose, Dhasma compared two different doses of dexmedetomidine: 1 μcg/kg and 1.5 μcg/kg, and he found that both doses can produce effective sedation with protection of airway reflexes.[12]

In our study, we compared the first standard dose (1 μcg/kg) with a higher dose (2 μcg/kg) to demonstrate if increasing the dose of dexmedetomidine to that level can still cause more favorable outcomes, but we found that at this high dose a significant undesirable increase in the possibility of airway obstruction was found despite improvement in limb movement scores during intubation. The increasing scores of airway obstruction in Group D2 in this study did not result in oxygen desaturation as it was managed by airway opening maneuvers as chin lift and jaw thrust.

It was mentioned that high dose of dexmedetomidine could cause bradycardia, hypotension, hypoxia, and atrial fibrillation.[16] In our study, we found only bradycardia that was managed easily by atropine.

Fentanyl was compared with dexmedetomidine for sedation during AFOI in several previous clinical trials. In 2010, when a small dose of fentanyl (1 μcg/kg) was compared with a small dose of dexmedetomidine (1 μcg/kg) by Chu *et al*., a better tolerance to intubation was found in the favor of dexmedetomidine.[2] In 2015, Mondal *et al*. compared the same low dose of dexmedetomidine (1 μcg/kg) with a higher dose of fentanyl (2 μcg/kg), and they found that this higher dose of fentanyl caused more airway obstruction and consequent oxygen desaturation; however, still dexmedetomidine provides a more desirable tolerance to intubation in the form of less cough scores.[1] In our study, we combined the low dose of dexmedetomidine (1 μcg/kg) with a low dose of fentanyl (1 μcg/kg) to avoid respiratory depression associated with the use of fentanyl in Mondal *et al*. trial.

Limitations

One of the limitations of this study might be the relatively small sample size that could not show a statistical difference between groups (if actually present in population) regarding intubation comfort scores. Another limitation is the absence of a postoperative feedback from the patients measuring their satisfaction about the sedation regimen used during their intubation.

Conclusion

In brief, increasing the dose of dexmedetomidine to 2 μcg/kg can result in more possibility of airway obstruction; however, this high dose achieves good intubation scores similar to that achieved by the use of a combination of low doses of dexmedetomidine and fentanyl. The addition of a low dose fentanyl (1 μcg/kg) to a low dose of dexmedetomidine results in improvement of limb movement scores during intubation with preservation of airway patency.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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