Use of dexemedetomidine–fentanyl versus midazolam–fentanyl for sedation during awake fiberoptic intubation: a randomized double-blind controlled study

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Background and objective
Sedation for awake fiberoptic intubation is considered a great challenge for anesthetist to maintain patient's airway patent during sedation. The aim of this study is to compare the effect of dexmedetomidine–fentanyl versus midazolam–fentanyl combination on patient's ventilation during sedation for awake fiberoptic intubation.
Patients and methods
A total of 60 patients, 20–60 years old, with American Society of Anaesthesiologists classification I and II, were enrolled in the study to be scheduled for awake nasal fiberoptic intubation for cervical spine surgery. Patients were divided into two groups. Group 1 received fentanyl 1 μg/kg, intravenously+midazolam, intravenously, 0.05 mg/kg followed by saline infusion (placebo) with additional doses of midazolam (0.05 mg/kg) to achieve a Ramsay Sedation Scale score of greater than or equal to 2. Group 2 received fentanyl 1 μg/kg, intravenously +dexmedetomidine, intravenously, 1 μg/kg infusion over 10 min, and then the infusion of dexmedetomidine 0.1 μg/kg/h and titrated to 0.7 μg/kg/h to achieve Ramsay Sedation Scale greater than or equal to 2.
Measurements
Vital signs (heart rate, systolic blood pressure, and oxygen saturation) as well as respiratory rate were recorded. Arterial blood gases sampling was done before and after the intubation. The Observer's Assessment of Alertness/Sedation Scale was used to assess the level of sedation. The visual analog scale used to assess patients' recall and discomfort, and finally, time to intubation in both groups was also recorded.
Results
There was significant decrease in heart rate, no difference in systolic blood pressure, and significant increases in SpO_2 and PaO_2, with preservation of patient's ventilation in dexmedetomidine group. No difference was noted in visual analog scale score or time to intubation between both the groups.
Conclusion
Dexmedetomidine provided better intubating conditions, better patient tolerance, higher patient satisfaction, and good hemodynamic responses compared with midazolam, with preservation of arousability in addition to better ventilation properties.

Keywords:
awake fiberoptic intubation, dexmedetomidine, midazolam, sedation

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Introduction

Large numbers of patients are candidates for surgical procedures, and some of them need planning for their airway management. Among these patients include those scheduled for spinal surgeries owing to trauma, malignancy, or degenerative diseases. The main anesthetic challenge is to provide safe anesthetic management while keeping adequate perfusion and oxygenation to the patient and maintaining spinal cord stabilization during intubation. Awake fiberoptic intubation (AFOI) is indicated for patients with anatomical problems, trauma of the airway, unstable cervical spine injuries, or morbid obesity [1]. Patients should be sedated for AFOI, but they should be kept responsive while maintaining their airway patent without assistance. This procedure could be complicated by hypoxia and aspiration [2]. Most of the literature is focused on patient's sedation and discomfort, but in our study, we focused on patient's ventilation and oxygenation during sedation by the proposed drugs combination.

Dexmedetomidine is a highly specific, potent, and selective α_2 adrenoceptor agonist. It has sedative, analgesic, and anesthetic-sparing effect [3]. It decreases sympathetic nervous system activity in a dose-dependent fashion. Moreover, it has the potential to exert inhibitory effects on cortisol and catecholamines synthesis. It does not cause respiratory depression and also decreases salivary secretions during sedation [4].

We assumed that using dexmedetomidine–fentanyl mixture will be better than midazolam–fentanyl mixture in AFOI, providing proper sedative, analgesic effects without impairing ventilation, and improving patient's responsiveness and co-operation as well as achieving better control of hemodynamics.

Patients and methods

After approval of the Ethical Committee, this study was conducted at Kasr El Ainy and Fayoum University Hospitals. Each patient signed a full written informed consent before participation in this trial.

A total of 60 patients with physical status American Society of Anaesthesiologists I and II scheduled for awake nasal fiberoptic intubation for cervical spine surgery were enrolled in this study. Patients were randomly allocated in one of two groups using computer-generated tables. In group 1, 30 patients were scheduled to receive sedation with midazolam–fentanyl. In group 2, 30 patients were scheduled to receive sedation with dexmedetomidine–fentanyl. Patients included in this study had nonmalignant pathology and were aged between 18 and 60 years old. Any patient who refused the technique was excluded from the study. Other causes of exclusion of patients were obesity, gastroesophageal reflux disease, reactive airway disease, drug abuse, or hypersensitivity to any of the used drugs.

Routine preoperative investigations were done. All patients fasted for at least 6 h before the operation and received 500 ml of Ringer's solution, intravenously, 1 h before the operation. Usual monitoring was used [ECG, noninvasive blood pressure, pulse oximeter (SpO_2), and capnography]. Cannulation of the radial artery of the nondominant hand was performed using local anesthetic infiltration for both blood pressure monitoring and blood gases analysis.

All patients were premedicated with atropine 0.2 mg intravenously 15 min before the start of the procedure. Group 1 received fentanyl 1 μg/kg intravenously +midazolam intravenously 0.05 mg/kg followed by saline infusion (placebo) with additional doses of midazolam to achieve a Ramsay Sedation Scale (RSS) [5] score of greater than or equal to 2 (Table 1). Group 2 received fentanyl 1 μg/kg intravenously+dexmedetomidine intravenously infusion 1 μg/kg over 10 min, and then an infusion of dexmedetomidine 0.1 μg/kg/h and titrated to 0.7 μg/kg/h to achieve RSS greater than or equal to 2.

The nasal mucosa of both nostrils was prepared with a vasoconstrictor and lidocaine 2% spray. Both nostrils were probed with nasopharyngeal tubes (covered with lidocaine gel 2%), and the more patent nostril was chosen for intubation, whereas the other nostril was used for oxygen insufflation (3–4 l/min). After removal of the nasopharyngeal tube, an ETT tube (7–7.5 mm in diameter in men and 6– 6.5 mm in diameter in women) was guided into trachea using the fiberoptic bronchoscope. During the procedure, 3 ml of lidocaine 2% was sprayed on the supraglottic region through the working channel of the bronchoscope. Additionally, 3 ml of lidocaine 2% was sprayed on the vocal cords immediately before the passage of the fiberoptic bronchoscope (FOB) +3 ml of lidocaine 2% was injected into trachea once fiberoptic tube passes through vocal cords. After sliding the ETT in place, confirmation of the tube position was done with capnography reading. General anesthesia was then induced by propofol 1–2 mg/kg intravenously and atracurium 0.5 mg/kg.

The Observer's Assessment of Alertness/Sedation Scale (OAA/S) [6] (Table 2) was used to assess sedation by measuring four components categories, and the summed score was assigned. OAA/S was determined before the start of the study medications and every 2 min during airway manipulation. Arterial blood samples for blood gas analysis were drawn at baseline and every 2 min throughout the airway manipulation. Hemodynamics [heart rate (HR), noninvasive blood pressure and SpO_2) and respiratory rate were recorded at baseline and every

Table 1 Ramsey sedation scale [5]

Score	Definition
1	Anxious, agitated or restless.
2	Cooperative, oriented and tranquil.
3	Responds to commands only.
4	Asleep but with brisk response to light, glabellar tap or loud auditory stimuli.
5	Asleep but sluggish response to light, glabellar tap or loud auditory stimuli.
6	Asleep, no response

3 min till intubation and then every 5 min till 20 min after intubation. Time from injection of drugs to intubation was also recorded. On the first postoperative day, an investigator blinded to the protocol evaluated the patients on their recall and level of discomfort during fiberoptic intubation. The visual analog scale (VAS) score from 0 to 100 described 'no recall' to 'perfect recall' and 'no discomfort' to 'extreme discomfort' [7].

Statistical analysis

Data were collected, coded, and translated to English to facilitate data manipulation and double entered into Microsoft Access, and data analysis was performed using SPSS software, version 18, under Windows 7 (IBM Corp., Chicago, USA). Simple descriptive analysis was done in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, SDs as measure of dispersion for quantitative parametric data, and inferential statistic test were performed.

For quantitative parametric data

Independent Student's *t*-test was used to compare measures of two independent groups of quantitative data.

For quantitative nonparametric data

Mann–Whitney test was used for comparing two independent groups.

For qualitative data

χ^2-Test was used to compare two of more than two qualitative groups. *P*-value less than or equal to 0.05 was considered as the cut-off value for significance.

Sample size calculation

We were planning a study of a continuous response variable from independent control and experimental patients with one control(s) per experimental patient. In a previous study, the response within each patient group was normally distributed with SD of 1.3. If the true difference in the experimental and control means is 1, we will need to study 28 experimental patients and 28 controls to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 0.8. The type I error probability associated with this test of this null hypothesis is 0.05.

Results

There was no difference between the two study groups (midazolam and dexmedetomidine) regarding age, weight, and sex, with *P*-value less than 0.05 (Table 3).

There was a significant difference between the two study groups regarding HR (decreased more in dexmedetomidine group) before intubation, with *P*-value less than 0.05 (Fig. 1). There was a significant

Table 2 Observer's assessment of alertness/sedation scale

Responsiveness	Assessment categories			Composite score level
	Speech	Facial expression	Eyes	
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5
Lethergic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words			2
Does not respond to mild prodding or shaking				1

Table 3 Comparison of age, weight, and sex between the two study groups

Variables	Group 1 (*n*=30)	Group 2 (*n*=30)	*P*-value	Significance
Age (mean±SD) (years)	52.3±4.8	54.4±3.9	0.06	NS
Weight (mean±SD) (kg)	89±11.6	86.6±7.2	0.3	NS
Sex [*N* (%)]				
Male	21 (70)	19 (63.3)	0.8	NS
Female	9 (30)	11 (36.7)		

*Indicates statistical significance difference with *P*-value <0.05. Data are expressed as mean ± standard deviation.

difference between the two study groups regarding systolic blood pressure at the follow-up of only 6 min from baseline (more in group 2), which is clinically not significant, with *P*-value less than 0.05 (Fig. 2).

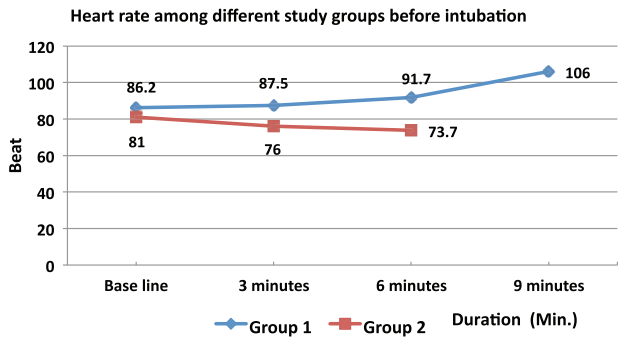
There was a statistically significant difference between the two study groups regarding respiratory rate at the follow-up of 3 and 6 min from baseline, with higher mean in the dexmedetomidine group, with *P*-value less than 0.05 (Table 4). There was statistically significant difference between two study groups regarding SpO_2% at follow-up of 3 and 6 min from baseline, with higher mean in dexmedetomidine group, with *P*-value less than 0.05 (Table 5). There was a statistically significant difference between the two study groups regarding PaO_2 at follow-up of 2–8 min from baseline, with higher mean among dexmedetomidine group, with *P*-value less than 0.05 (Table 6). There was a statistically significant difference between the two study groups regarding $PaCO_2$ at 4 min from baseline during intubation, with higher mean among midazolam group, with *P*-value less than 0.05 (Fig. 3).

There was a statistically significant difference between the two study groups regarding OAA/S level at the follow-up of 2–6 min from baseline, with higher mean among dexmedetomidine group, with *P*-value less than 0.05 (Fig. 4). There was no difference regarding time of intubation or VAS score in both the groups, with *P*-value greater than 0.05 (Table 7).

Discussion

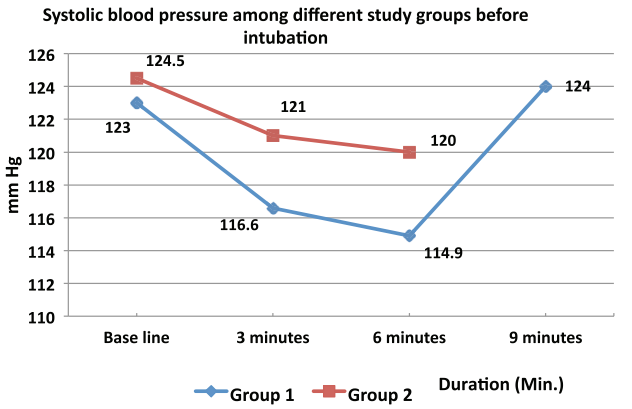
In this study, we reported equivalent sedation levels in both the groups using the designed study regimens. We used the RSS to start the procedure with the same sedation level in both groups; therefore, any differences between

Figure 1



Comparisons of heart rate among two study groups. *Indicates statistical significance difference with *P*-value <0.05.

Figure 2



Comparisons of systolic blood pressure among two study groups. *Indicates statistical significance difference with *P*-value <0.05.

Table 4 Comparisons of respiratory rate between the two study groups

RR/min	Group 1 (*n*=30)		Group 2 (*n*=30)		*P*-value	Significance
	N	Mean±SD	*N*	Mean±SD		
Baseline	30	12.5±2.1	30	11.9±0.96	0.2	NS
After 3 min	30	10.8±1.4	30	11.9±0.54	<0.001*	HS
After 6 min	20	10.7±0.5	21	11.8±0.85	0.001*	HS
After 9 min	3	14±0	0	–	–	–

HS, highly significant; RR, respiratory rate. *Indicates statistical significance difference with *P*-value <0.05. Data are expressed as mean ± standard deviation.

Table 5 Comparisons of SpO_2% between the two study groups

SpO_2%	Group 1 (*n*=30)		Group 2 (*n*=30)		*P*-value	Significance
	N	Mean±SD	*N*	Mean±SD		
Baseline	30	0.978±0.01	30	0.98±0.01	0.5	NS
After 3 min	30	0.95±0.02	30	0.976±0.01	<0.001*	HS
After 6 min	20	0.947±0.03	21	0.98±0.01	<0.001*	HS
After 9 min	3	0.97±0	0	–	–	–

HS, highly significant. *Indicates statistical significance difference with *P*-value <0.05. Data are expressed as mean ± standard deviation.

Table 6 Comparison of PaO_2 between the two study groups

PaO_2	Group 1 (n=30)		Group 2 (n=30)		P-value	Significance
	N	Mean±SD	N	Mean±SD		
Baseline	30	87.4±3.9	30	86.6±4.3	0.5	NS
After 2 min	30	85.2±3.8	30	87.2±3.6	0.04*	S
After 4 min	30	83.3±4.9	30	87.1±3.7	0.001*	HS
After 6 min	20	84.7±5.5	21	88.1±2.8	0.03*	HS
After 8 min	3	85±0	0	–	–	–

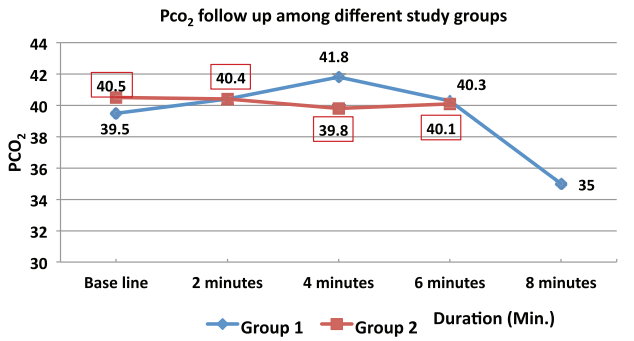
HS, highly significant; S, significant. *Indicates statistical significance difference with P-value <0.05. Data are expressed as mean ± standard deviation.

Table 7 Comparison of time of intubation between the two study groups

Variables	Group 1 (n=30) Mean±SD	Group 2 (n=30) Mean±SD	P-value	Significance
Time of intubation (min)	5.1±1.5	5.6±0.9	0.1	NS
VAS%	0.02±0.007	0.02±0.008	0.9	NS

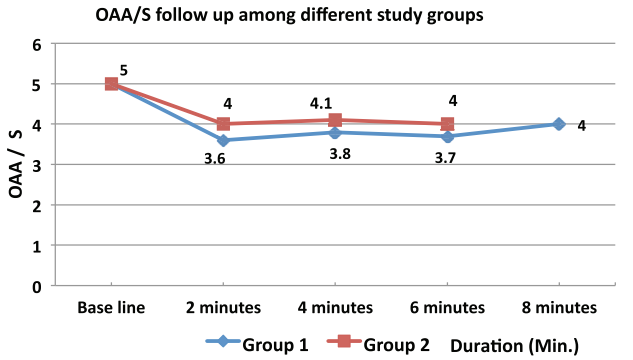
VAS, visual analog scale. *Indicates statistical significance difference with P-value <0.05. Data are expressed as mean ± standard deviation.

Figure 3



Comparison of $PaCO_2$ between the two study groups. *Indicates statistical significance difference with P-value <0.05.

Figure 4



Comparison of Observer Assessment of Alertness/Sedation Scale before and over the duration of the operation between the two study groups. *Indicates statistical significance difference with P-value <0.05.

the studied groups in the intubating conditions can be attributed to the pharmacodynamics of the sedative drugs. Fiberoptic intubation in fully awake patients often results in poor comfort and cooperation, which may induce technical difficulties and failure of the procedure [8]. We measured the OAA/S, during the procedure to compare the patient's response and facial expression during the procedure itself.

This study showed a difference regarding HR follow-up before intubation, with higher mean among midazolam group. HR decrease in this study may be because of high vagal tone, stimulation of baroreceptor response in high vascular tone with bolus injections, and/or decreased level of circulating norepinephrine. Although atropine was given as premedication, which is required to decrease secretion during AFOI, it was given to all patients in both groups, and the dose given was small.

Other publications matching our results include Prommer [9] who compared dexmedetomidine with midazolam for sedation of 375 ICU mechanically ventilated patients and revealed that dexmedetomidine was associated with a greater incidence of bradycardia. Gupta *et al.* [10] compared dexmedetomidine versus propofol premedication for fiberoptic intubation in patients with temporomandibular joint ankylosis and found that the HR decreased significantly in the dexmedetomidine group at the end of drug infusion. In another study of using sedation during noninvasive mechanical ventilation with dexmedetomidine versus midazolam, though baseline measurements of HR between groups were not significantly different, the patients in dexmedetomidine group had significantly lower HR levels compared with patients in midazolam group throughout the study period [11].

On the other hand, results of bradycardia were not significant while comparing dexmedetomidine with

placebo or with other anesthetics (e.g. remifentanil, sufentanil, propofol, or midazolam) as published by many RCTs [12].

There was a statistically significant difference regarding systolic blood pressure at follow-up after 6 min from baseline reading, with higher mean among dexmedetomidine group, but it was not considered clinically significant as it was just one reading. Systolic blood pressure increase in dexmedetomidine group may be due to large loading dose that may lead to stimulation of α2 receptors and vasoconstriction of blood vessels as was described by Bloor *et al.* [13].

On the contrary, Bergese *et al.* [2] compared dexmedetomidine plus midazolam versus midazolam alone, and he noticed no difference in both groups regarding systolic blood pressure. This may be because of using loading dose of 1 μg/kg infused over 15 min (longer duration then our study) followed by a small infusion dose of 0.2 μg/kg/h and titrated to 0.7 μg/ kg/h. Jorden *et al.* [14] as well noticed that high bolus dose of dexmedetomidine does not cause hypertension.

In contrast to our study results, a previous study of dexmedetomidine used as the sole sedative for awake intubation in management of the critical airway found that hemodynamic adverse effects such as hypotension were acceptable, and only two patients required treatment [15]. In a previous study of hemodynamic characteristics of midazolam, propofol, and dexmedetomidine in healthy volunteers observed a significant dose-dependent blood pressure reduction with dexmedetomidine. Blood pressure reduction continued into recovery 20 min after the infusion was discontinued [16]. This may be owing to stimulation of baroreceptor response in high vascular tone with bolus injection and or decreased level of circulating norepinephrine.

There was also a statistically significant difference regarding respiratory rate at follow-up of 3 and 6 min from baseline readings, with higher mean in dexmedetomidine group. There was a statistically significant difference regarding SpO_2% at follow-up of 3 and 6 min from baseline readings, with higher mean among dexmedetomidine group. In line with our results, Abdelmalak *et al.* [15] and Venn *et al.* [4] showed no statistically significant difference when comparing dexmedetomidine with placebo regarding respiratory rate, and even less respiratory depression when comparing dexmedetomidine with other drugs (remifentanil, sufentanil, propofol, or midazolam) [12]. Moreover, Singh *et al.* [17] compared dexmedetomidine versus midazolam sedation for AFOI and found that oxygen saturation and $PaCO_2$ were maintained in dexmedetomidine group.

In contrast to this study, Cooper *et al.* [18] revealed there was no statistical or clinical difference between dexmedetomidine, midazolam, and opioids for oxygenation, with all patients at all-time saving a pulse oximeter value of 97% or greater. Moreover, Senoglu *et al.* [11] showed no statistically significant difference in respiratory rate between dexmedetomidine and midazolam when used for sedation during noninvasive ventilation. It may be because of the use of small doses of midazolam infusion (0.1 mg/kg/h).

Regarding OAA/S level, there was no clinical significant difference between the groups, and same finding was confirmed also by Bergese *et al.* [2].

There was no difference regarding time to intubation between study groups. This goes in line with results of Bergese *et al.* [2] who found that there was no statistical significant difference between midazolam group versus dexmedetomidine plus midazolam group in time to intubation (from insertion of fiberoptic to first reading of capnography).

There was no difference regarding VAS level between study groups, which means more cooperative patients without difference in patient's recall and satisfaction. This goes in line with results of Singh *et al.* [17].

Moreover, Bergese *et al.* [2] found that there were no difference between midazolam group versus dexmedetomidine and midazolam group in recall, but patients treated with dexmedetomidine plus midazolam were more satisfied than those treated with midazolam only.

The limitation of our study was the small number of patients included in the study. Moreover, in future studies, we can use different concentrations of dexmedetomidine and evaluate their effects on blood pressure and HR.

Recommendations

(1) Further studies on a larger number of patients are needed to confirm the finding of this study.
(2) Additional studies are needed to further clarify the role of dexmedetomidine as a sole agent for sedation in procedures requiring conscious sedation.

Conclusion

Dexmedetomidine provided better patient tolerance, higher patient satisfaction, and reduced hemodynamic responses than midazolam. It has anxiolytic, sedative, amnesic, and analgesic properties that can add to the patient's comfort, enabling greater tolerance to the procedure. The major advantage was preservation of arousability and respiratory-sparing properties.

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Nil

Conflicts of interest

There are no conflicts of interest.

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