Original article

Comparison of the safety and effectiveness of dexmedetomidine with a combination of midazolam and fentanyl for sedation during awake fibreoptic nasotracheal intubation

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Abstract

Introduction: Several drugs have been used to enhance patient comfort during awake nasal fibreoptic intubation (AFOI) process. Most of these can cause dangerous airway or haemodynamic compromise. This study compared combination of midazolam and fentanyl against dexmedetomidine. **Methods:** Thirty two adults undergoing AFOI were randomly allocated into group MF (1mg midazolam and 1 µg/kg fentanyl) or group D (dexmedetomidine 1µg/kg over 10 minutes). Following standard airway topicalisation technique, the study drugs were administered and AFOI was performed. **Results:** The demographic data, patient comfort score, post intubation score, endoscopy and intubation times were comparable. The endoscopy was observed to be easy in all patients except 2 in MF group while intubation was easy in all (group D) versus 12 patients in group MF (P value 0.03). Significant haemodynamic response was observed in group MF while patients were more stable in group D. Postoperatively, 10 and two patients in groups D and MF respectively felt sedation was excellent (P value 0.02) while increased need for sedation was felt by one and three patients in groups D and MF respectively (P value 0.028). AFOI was remembered by six and one patients in groups D and MF respectively (P value 0.003). Two in group D and three in group MF had moderate discomfort. None experienced severe discomfort. The overall satisfaction score was comparable. There were no serious adverse events during the study. **Conclusions:** Dexmedetomidine provides better intubating conditions and patient satisfaction without adversely affecting the airway or haemodynamic stability during AFOI.

Keywords: Awake fibreoptic intubation, dexmedetomidine, fibrescopy, sedation.

Introduction

General anaesthesia involves administration of the anaesthetic agents to render the patient unconscious, control of the airway and then instrumentation of the airway to assist or provide artificial ventilation. Once the patient is rendered unconscious, the respiration is depressed to a variable degree while the structures of the oral cavity tend to obstruct the nasopharyngeal and oropharygneal passages to a variable degree. Therefore, it is vital that the anaesthesiologist is able to take control of the patient's airway. Airway and respiration are usually controlled by the anaesthesiologist with minimal discomfort. However, inability to control the airway after induction of anaesthesia can happen, *albeit* rarely, which can have serious consequences on the patient's life. Therefore, meticulous assessment of the airway in the preoperative period is very important. When a recognised difficult airway is

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present, safe option is to achieve tracheal intubation while the patient's consciousness and respiratory drive are still well intact. This is generally referred to as *awake intubation.*

Decades ago, blind nasal intubation or retrograde intubation were the only options left for the anaesthesiologists other than considering a surgical tracheostomy when dealing with recognised difficult airway. However, with advancement of science and technology, fibreoptic bronchoscope was developed. Subsequently, awake fibreoptic intubation (AFOI) has become the accepted gold standard technique for management of a recognised difficult airway.[1] Integral part of any awake intubation technique is to ensure minimal discomfort to the patient by administering sedatives or analgesics or a combination of both without compromising safety. An ideal sedative drug for awake intubation should ensure the patient remains reasonably conscious to protect the airway and maintain spontaneous ventilation, while at the same time it must ensure a calm and co-operative patient by providing adequate anxiolysis and analgesia. Several analgesics (fentanyl, remifentanil) and sedatives (midazolam, propofol) have been used that can improve patient comfort and tolerance of the awake fibreoptic intubation process.[2-7] However, if these drugs have to be administered in dosages that can provide excellent comfort for the patients during awake fibreoptic intubation, there are high chances that the patient may have respiratory depression and obtundation of sensorium resulting in untoward adverse effects such as hypoxaemia, airway obstruction, *etc.*[2,8-10] Therefore, there is a need to find alternative pharmacological agents that can provide equally good or even better patient comfort without compromising on patient safety. Recently, there are reports of dexmedetomidine, a selective α_2 agonist that provides both sedation and analgesia without causing respiratory depression or airway compromise.[11-14]

In our department, it is a standard practice to use fentanyl and midazolam combination to provide sedation and analgesia during awake nasal fibreoptic intubation for recognised difficult airway. Therefore, in this study, we compared the safety and effectiveness of dexmedetomidine versus a combination of fentanyl and midazolam for awake nasal fibreoptic intubation in patients with recognised difficult airway.

Methods

After obtaining Institutional Ethics Committee approval, patients aged above 18 years with recognised difficult airway scheduled to undergo awake nasal fibreoptic intubation were identified, the methodology was discussed and written informed consent was obtained from those willing to participate in the study. Haemodynamically unstable patients (bradycardia with heart rate < 50 bpm or hypotension with systolic blood pressure < 90 mm Hg), patients who were seriously ill (American Society of Anesthesiologists' grade 4), those with known coronary artery disease, impaired liver function, those on therapy in the previous two weeks with either $\alpha_2$agonist or antagonist, those having raised intracranial pressure, uncontrolled seizure disorder and/or a known psychiatric illness were excluded from the study. A total of 32 patients were included in the study. The study was prospective, double blinded and randomised in nature. The randomisation was done using an open label computer generated randomisation table.

All patients received anti-aspiration prophylaxis in the form of oral Ranitidine 150 mg and Metoclopramide 10 mg night before and on the morning of surgery. No other sedative premedication was administered. Prior to surgery, an intravenous (IV) access was established, crystalloid infusion started and IV glycopyrrolate 0.2 mg was administered after establishing monitoring (5 lead electrocardiogram, non invasive blood pressure and SpO_2) and recording baseline vitals. Then two drops of oxymetazoline (0.05%) was instilled in each nostril of the study subject. Approximately 15 minutes later, patients were also asked to gargle with lignocaine viscous 2% (5 mL) and nostrils were packed with gauze soaked in 4% lignocaine (5 mL). After this, the patients were shifted to operating room. The monitoring was continued in the operating room. Serial dilatation of the nostril that had best patency was performed with increasing sizes of nasopharyngeal airway that were lubricated with lignocaine jelly.

An anaesthesiologist prepared the study drugs as per the randomisation table. This person did not have any further involvement with the study to ensure blinding. The details of study drug preparation are given below:

Group D: Patients in this group received 1 μg/kg of dexmedetomidine (diluted to a volume of 20 mL with normal saline) over 10 minutes. Syringe A (20 mL syringe) containing dexmedetomidine 1 μg/kg (rounded off to the nearest multiple of 5) diluted to 20 mL with saline, was infused over 10 minutes (120 mL/h). A 50 cm extension tubing (with a dead space of 4 mL) was used to infuse the contents from the syringe to a three-way tap placed directly connected to an intravenous cannula. At the end of injection of this 20 mL, another 5 mL saline was injected into the 20 mL syringe and run at the same rate to ensure no drug remained in the dead space of the infusion line. Syringe B containing 2 mL of saline, 1 mL of this was injected at the 5th min. Syringe C containing 2 mL of saline, (0.02 mL/kg) was injected at the 9th min.

Group MF: Patients in this group received midazolam and fentanyl for sedation. Syringe A (20 mL syringe) containing saline (20 mL) was infused over 10 minutes (120 mL/h). A 50 cm extension tubing (with a dead space of 4 mL) was used to infuse the contents of the syringe to a three-way tap placed directly connected to an intravenous cannula. At the end of injection of this 20 mL, another 5 mL saline was injected into the 20 mL syringe and run at the same rate to ensure no drug remained in the dead space of the infusion line. Syringe B containing 1 mL of midazolam (1 mg/mL) was injected at the 5th min. Syringe C containing 2 mL of Fentanyl, (50 μg/mL = 0.02 mL/kg = 1 μg/kg, rounded off to the nearest multiple of 5 was injected at the 9th min.

Rescue drug: Midazolam 1 mg/mL was kept in open label syringes for use if the patient was found to be restless during the study. This was left to the discretion of the person doing fibreoptic intubation during the study. Use of rescue drug or any adverse effects were recorded.

Description of protocol for awake nasal fibreoptic intubation:

Fibreoptic scope of 3.5 mm insertion cord diameter (FI-10BS/10RBS Pentax™ Corporation, Tokyo, Japan) was used for the study. Cuffed tracheal tubes (Portex) of suitable size (7.0 or 7.5 mm ID and 6.0 or 6.5 mm ID) were mounted onto the fibrescope for men and women respectively. Immediately at the end of the study drug infusion, awake fibreoptic intubation was performed with the oxygen (2 L/min) connected to the injection port. Once the glottic structures were identified, 2 mL 2% lignocaine was sprayed (through a three-way tap in the oxygen tubing) on to the vocal cords. About a minute later, the fibrescope was advanced into the trachea where another 2 mL of 2% lignocaine was instilled and about a minute later, the tracheal tube was advanced over the fibrescope. General anaesthesia (GA) was induced after confirming appropriate positioning of the tracheal tube with fibreoptic visualisation, waveform capnography and auscultation for bilateral equal air entry.

The primary outcome measures included the patient comfort score during fibrescopy and intubation as assessed based on five different parameters, post intubation score, the intubator's perception of ease of performing the fibrescopy and intubation as well as the postoperative questionnaire (24 h after the procedure) to evaluate patient's own assessment of the comfort during the procedure. (*Table 1*) Secondary outcome measures included the fibrescopy time (time from introducing the fibrescope into patient's nostril to visualisation of carina), intubation time (time from introducing the tracheal tube into the nostril till confirmation of tracheal intubation by waveform capnography), number of attempts (an attempt was from insertion of fibrescope into the nostril till withdrawal of the fibrescope out of the nostril either after intubation or due to some complication such as inability to intubate due to blood/secretion *etc*), haemodynamic responses to the process of intubation and any complication arising during the study.

Table 1: Primary outcome measures

Comfort score based on five parameters					
Parameter	**1**	**2**	**3**	**4**	**5**
Sedation	Awakens to voice (eye opening/contact) >10 sec	Light sedation, briefly awakens to voice(eye opening/ contact)	Moderate sedation, movement or eye opening. No eye contact	Deep sedation, no response to voice, but movement or eye opening to physical stimulation	Unarousable, no response to voice or physical stimulation
Agitaion	Alert and Calm	Anxious, apprehensive, but not aggressive	Frequent nonpurposeful movement	Pulls or removes tube (s); aggressive	Combative, violent
Respiratory Response	Spontaneous respiration	Occasional cough	Coughing regularly	Frequent coughing or choking	Cough preventing insertion of scope ETT
Physical Movement	No movement	Occasional slight movement	Frequent slight movements	Vigorous movement limited to the extremities	Vigorous movements including torso and head
Facial Tension	Facial muscle tone normal, no facial muscle tension evident	Tension evident in some facial muscles	Tension evident throughout facial muscles	Facial muscles contorted and grimacing	Grimacing and crying
Post intubation score					
Score 1: Co-operative and calm Score 2: Restless, minimal resistance Score 3: Severe resistance, general anaesthesia required immediately					
Postoperative questionnaire					
a) How was the sedation for your procedure? 1 = Excellent 2 = Good 3 = Fair 4 = Poor b) Do you think you needed any adjustment in the amount of sedation you received? 1 = No 2 = Yes c) Do you remember being awake during the procedure? 1 = No 2 = Yes d) How much discomfort or pain did you experience during the procedure? 1 = None 2 = Mild 3 = Moderate 4 = Severe e) Overall, using this numerical rating scale, where 0 is complete satisfaction and 10 is complete dissatisfaction, how would you rate your satisfaction with your intubation? 0 = Complete satisfaction 10 = Complete dissatisfaction					

Results

To obtain 90% power of the study for a difference of two points in the comfort score recorded during the study with an alpha error of 5%, a total of 32 patients (16 in each group) were needed to be included in the study.

A total of 32 patients participated in the study, 16 in group MF (midazolam-fentanyl) and 16 in group D (dexmedetomidine). All patients completed the study. All the patients belonged to ASAPS 1 or 2. The patient's age ranged from 18 -72 years. There were a total of 15 men in group MF and 14 men in group D while the rest were women. The demographic data was comparable between the groups (*Table 2*).

Table 2: Demographic data

PARAMETER	GROUP MF (n = 16)	GROUP D (n = 16)	p value**
Age (years) Mean ± SD	42.50 ± 19.22	46.69 ± 14.33	0.49 (NS)
Weight (kg) Mean ± SD	57.31 ± 16.5	54.69 ± 12.9	0.622 (NS)
Height (metres) Mean ± SD	1.65 ± 0.058	1.64 ± 0.067	0.619 (NS)
Body Mass index (kg/m^2) Mean ± SD	20.68 ± 5.28	19.98 ± 3.65	0.665 (NS)

** Independent Samples test (NS)= not significant

Comfort scores were categorised into four groups where a score of 5-6, 7-13, 14-18 and > 19 represented

excellent, good, poor and very poor conditions for either fibrescopy or intubation. The scores were compared using Chi square test for both fibrescopy and intubation. Results showed no statistically significant difference in comfort scores between the two groups during fibrescopy or intubation (*Table 3*). The post intubation scores were also comparable between the two groups with only three patients in group MF and two in group D offering minimal resistance during intubation process and none in either group posed severe difficulty in advancing the tracheal tube into the glottis (*Table 3*).

Table 3: Comparison of comfort scores during fibrescopy and intubation

	Fibrescopy		Intubation	
	MF (n = 16)	D (n = 16)	MF (n = 16)	D (n = 16)
Excellent (5,6)	6	7	0	0
Good (7-13)	10	9	12	13
Poor (14-18)	0	0	4	2
Very poor (>18)	0	0	0	1
P value	0.719* (NS)		0.349* (NS)	
* = Chi square test NS = not significant				
Comparison of the post intubation scores				
Post intubation score	Group MF (n = 16)	Group D (n = 16)	P value	
1	13	14	0.625* (NS)	
2	3	2		
3	Nil	Nil		
* = Chi square test NS = not significant				

The fibrescopy time was comparable with 107.81 ± 53.02 seconds for group MF and 94.25 ± 45.20 seconds for group D (P value 0.304). Similarly, the intubation times were also comparable with 129.31 ± 100.85 seconds for group MF and 126.63 ± 90.134 seconds for group D (P value 0.612). Independent Samples test was used to do statistical analysis of these values. A total of 30 patients could be intubated in one single attempt while one patient in each group needed a second attempt for successful intubation.

The perception of the anaesthesiogist regarding difficulty in fibrescopy was comparable between the groups. However, the anaesthesiologist perceived intubation process to be easy in all patients belonging to group D while it was perceived to be difficult in four patients in group MF which was statistically significant (*Table 4*).

Table 4: Comparing the anaesthesiologist's perception of difficulty in fibreoptic scopy and intubation

Anaesthesiologist Difficulty perception (Fibrescopy)	GROUP MF (n = 16)	GROUP D (n = 16)	p value
EASY	14	16	0.14* (NS)
DIFFICULT	2	0	
Anaesthesiologist Difficulty perception (Intubation)	GROUP MF (n = 16)	GROUP D (n = 16)	p value
EASY	12	16	0.03**
DIFFICULT	4	0	

*Chi square test **statistically significant NS= not significant

The haemodynamic profile was mainly assessed (HR, MBP, SBP and DBP) at baseline, during fibrescopy and at completion of tracheal intubation. Within the group comparison showed a statistically significant increase in the HR, MBP and SBP at intubation compared to baseline value in group MF while the DBP change (fall from baseline) was statistically significant in group D during fibrescopy (*Table 5*).

Table 5: Haemodynamic changes during the procedure

		Group MF (n = 16)	Group D (n = 16)	P value
HR (bpm)	Baseline	88.06 ± 25.23	83.75 ± 17.55	MF 0.006*
	Fibrescopy	89.25 ± 20.71	77.56 ± 16.93	D 0.189 (NS)
	Intubation	101.19 ± 19.76	92.81 ± 22.51	
MBP (mm Hg)	Baseline	103.75 ± 12.38	109.37 ± 17.33	MF 0.021*
	Fibrescopy	102.50 ± 12.60	101.12 ± 18.06	D 0.391(NS)
	Intubation	112.87 ± 16.73	106.00 ± 17.93	
SBP (mm Hg)	Baseline	134.62 ± 21.59	139.87 ± 22.05	MF 0.034*
	Fibrescopy	133.25 ± 24.06	135.25 ± 29.41	0.344 (NS)
	Intubation	149.68 ± 25.21	143.25 ± 33.04	
DBP (mm Hg)	Baseline	86.38 ± 9.79	90.62 ± 15.88	
	Fibrescopy	81.31 ± 13.88	81.00 ± 16.54	MF 0.08 (NS)
	Intubation	86.75 ± 16.24	86.50 ± 16.66	D 0.04#
	Statistical test used: Repeated measure of Anova (*within the group* comparison)			
	* HR, MBP and SBP showed statistically significant difference in the values at intubation compared to baseline values in group MF. The changes were not significant in group D (NS). #However, patients in group D had statistically significant change in DBP at fibrescopy compared to baseline. The changes were not significant in group MF.			

The postoperative questionnaire

Ten patients in group D and two patients in group MF felt that the sedation quality was excellent (P 0.02). However, 13 and 14 patients each in group MF and D respectively felt the sedation quality was either excellent or good (clinically acceptable standard of sedation). Three patients in group MF

and one in group D felt that the sedation dose could have been increased (P value 0.028). Only one patient in group MF and six patients in group D remembered the process of fibrescopy and intubation 24 hours after the procedure (P = 0.003). When enquired as to how much discomfort they experienced during the process of intubation, 13 in group MF and 14 in group D felt the discomfort was either nil or mild. The others felt it was moderate and none felt the discomfort was severe in intensity (P = 0.885). When assessed on a scale of 0 to 10 with 0 being complete satisfaction and 10 being complete dissatisfaction, an average score of 4.00 ± 1.78 (group MF) and 2.94 ± 1.56 (group D) was obtained (P = 0.084) (*Table 6*).

No patient in either group had any hypoxaemia (SpO_2 < 92%), apnoea or hypopnoea (< 8 breaths per minute), obtundation of mentation to a state of unresponsiveness or extreme changes in heart rate or blood pressure (> 30% from baseline) requiring treatment.

Discussion

Awake fibreoptic intubation is the accepted gold standard technique for airway management of patients with recognised or anticipated difficult airway. Nasal route of intubation is preferred when the pathology contributing to difficult airway is in and around the oral cavity. Furthermore, nasal approach to fibreoptic intubation is relatively easier than the oral approach even in anaesthetised patients.[15] Although good topical anaesthesia to the airway can help suppress airway responses to awake fibreoptic intubation, an anxious patient can create considerable difficulty in performing fibrescopy and intubation. Good preoperative counselling and building nice rapport may help calm the patient to a certain degree. However, judicious use of sedatives/analgesics can certainly render the patient more co-operative and the procedure, a more pleasant experience. Several sedatives and/or analgesic drugs have been used to improve the intubating conditions, patient tolerance, comfort and satisfaction.

Dexmedetomidine, due to its good sedative and analgesic effects combined with lack of respiratory depressant effects has been gaining popularity for awake tracheal intubation.[5,14,16,17] In our study, we compared dexmedetomidine 1 μg/kg infused over 10 min prior to start of the fibrescopy and intubation versus midazolam 1 mg and fentanyl 1 μg/kg bolus. A total of 32 patients with anticipated or recognised difficult airway requiring awake fibreoptic guided nasotracheal intubation participated in the study (16 in each group). The patient comfort scores that were a composite of several aspects (*Table 1*) were acceptable (good to excellent) for fibrescopy in all the patients. However, the scores were acceptable in 25 patients (12 in group MF and 13 in group D) during intubation process. Although the comfort scores for intubation were unacceptable (poor or very poor) in 7 patients (4 in group MF and 3 in group D), none received rescue midazolam. This is because these scores were assessed at the end of the intubation process and hence they reflected conditions at that moment. However, these patients were comfortable till the tracheal tube entered the glottis indicating insufficient anaesthesia to the lower airway (infraglottic area and trachea). Rescue dose of midazolam was not administered at this juncture as general anaesthesia was induced soon after intubation was confirmed. Further analysis of the comfort scores showed that limb movements contributed mainly to poor scores in these patients. Similar incidences have been quoted in literature where topical anaesthesia to airway was given during the study.[14,17,18] Combining sedation and analgesia with transtracheal local anaesthetic instillation might be an interesting future research point to see if this can minimise patient responses to intubation. We did not consider recurrent laryngeal nerve block (transtracheal instillation of local anaesthetic) in our study, as we felt the noninvasive option of '*spray as you go*' was equally efficient.

Objective assessment of patient comfort (airway conditions for fibrescopy and intubation by performing anaesthesiologist) during the procedure revealed both dexmedetomidine and midazolam-fentanyl combination to be comparable and good. However, other studies have shown dexmedetomidine to provide superior patient comfort during fibrescopy and intubation compared to either midazolam infusion or fentanyl infusion

alone.[5,17,18] The time to intubation was comparable in all the studies including ours indicating adequate intubating conditions using these agents combined with topical airway anaesthesia. Differences in patient comfort during fibrescopy and intubation between our study and other studies may be because dexmedetomidine provides both sedation and analgesia while midazolam, fentanyl or propofol when administered as sole agent for awake intubation cannot simultaneously provide both elements. Since our study involves use of both midazolam for sedation and fentanyl for analgesia, the patient conditions for fibrescopy and intubation appear to be comparable with that of dexmedetomidine. Fentanyl, in addition to providing analgesia, might have also contributed to better suppression of the airway reflexes along with topical anaesthesia. Our study also involved evaluation of airway conditions during fibrescopy and intubation by the anaesthesiologist performing the intubation procedure. Their assessment showed that patients in the dexmedetomidine group had better airway conditions for fibrescopy and intubation (easy conditions in all patients) whereas difficult conditions for fibrescopy and intubation were observed with midazolam-fentanyl combination in two and four patients respectively.

In our study, haemodynamics (heart rate and blood pressure) were analysed at three time points (baseline, fibreoptic scopy and intubation). It was found that there was statistically significant increase in the HR, SBP and MBP at intubation in group MF compared to baseline values. Haemodynamics were more stable in group D except for a statistically significant fall from baseline in DBP at fibrescopy which was restored to baseline by the time intubation was achieved. However, none of these haemodynamic fluctuations in either group were clinically significant enough to require treatment. These results are comparable with other studies although patients in the dexmedetomidine group needed transient haemodynamic support in one study.[5,17,18]

In our study, all patients were asked to answer a questionnaire 24 h after the surgery to assess their comfort during fibrescopy and intubation. This evaluation was done to ensure that the patients were not under any residual effects of anaesthetic agents during this survey. All patients opined that sedation during endoscopy and intubation was acceptable (excellent, good or fair) except one (poor sedation) in group MF. However, when asked if they felt the sedation dose could have been increased, three in group MF and one in group D answered in the affirmative (P 0.028). When patients were asked to evaluate the discomfort experienced during fibrescopy and intubation process on a scale of 10 (1 is minimum and 10 is maximum discomfort), dexmedetomidine was found to provide better patient comfort (5 patients with score ≥ 4) as compared to midazolam-fentanyl combination (11 patients with score ≥ 4). Majority of the patients in the midazolam-fentanyl group did not remember the procedure of fibrescopy and intubation (15 in group MF and 6 in group D, P 0.003). A study that used higher doses of midazolam showed lower incidence of recall that was comparable with the study group (dexmedetomidine-midazolam).[5] Therefore, it appears that the higher number of patients remembering the procedure in group MF in our study is attributable to the small dose of midazolam used for sedation. The incidence of recall was higher with dexmedetomidine compared to target controlled infusion of propofol whereas dexmedetomidine provided better amnesia than fentanyl.[17,18] Patients judged dexmedetomidine to be more satisfactory and comforting for the procedure than fentanyl or midazolam,[5,17] while patient satisfaction was comparable with target controlled infusion of propofol.[18] However, propofol was found to cause higher levels of intraoperative sedation resulting in increased airway obstruction that was not observed with dexmedetomidine.[18]

There were no significant haemodynamic or respiratory adverse events in our study. Therefore, we conclude that dexmedetomidine in a dose of 1 μg/kg when administered over 10 min prior to nasal AFOI, provides better airway conditions for anaesthesiologist and better patient satisfaction without adversely affecting the airway or haemodynamic stability.

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