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CLINICAL RESEARCH

Intubating conditions and hemodynamic changes during awake fiberoptic intubation using fentanyl with ketamine versus dexmedetomidine for anticipated difficult airway: a randomized clinical trial☆

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Abstract

Background and objectives: Awake fiberoptic intubation (AFOI) is usually performed in patients with an anticipated difficult airway. Various sedation regimens are used during AFOI, however, most of them cause respiratory depression. The present study aims to compare the effectiveness of fentanyl with ketamine versus dexmedetomidine in search of a better sedation regimen which would achieve desirable intubating conditions and hemodynamic stability without causing respiratory depression.

Methods: This is a single centered randomized, double-blind clinical trial. Patients of both sexes between age 18–55 years and ASA (American Society of Anesthesiologists) physical status I–II with an anticipated difficult airway were randomly divided into two groups of thirty each. Group FK patients received intravenous fentanyl and ketamine, and group DX patients received dexmedetomidine, until Ramsay sedation scale $\geq$ 2. Heart rate (HR), mean blood pressure (MBP), oxygen saturation (SpO_2), respiratory rate (RR), endoscopy time, intubation time, first end-tidal carbon dioxide ($ETCO_2$) after intubation, endoscopist satisfaction score, and patient discomfort score were recorded during the study period. The level of recall was assessed on the next postoperative day.

Results: Endoscopist satisfaction score was better in group DX patients ($p < 0.05$). There was a smaller variation in HR and MBP from baseline with dexmedetomidine compared to fentanyl with ketamine. First $ETCO_2$ after intubation was higher in group FK patients ($p < 0.05$). No significant difference was found in patient discomfort score, intubation time, RR, SpO_2 and level of recall of the event.

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Conclusions: The use of dexmedetomidine in AFOI provides better intubating conditions and hemodynamic stability compared to fentanyl with ketamine.

Introduction

Management of difficult airway is a routine affair for the anesthesiologists. A meticulous approach is paramount for its successful management. Awake fiberoptic intubation (AFOI) is considered the gold standard technique for the management of an anticipated difficult airway.[1] An ideal condition for AFOI requires a calm, cooperative patient with blunted airway reflex to facilitate easy intubation. Therefore, it is necessary to provide adequate anxiolysis, analgesia, and topical anesthesia for the airway without causing respiratory depression. Previously, various drug regimens either alone or in combinations has been tried for this purpose. However, most of them cause respiratory depression leading to airway obstruction, which is undesirable for AFOI.

Fentanyl with ketamine could offer hemodynamic stability with little respiratory side effects.[2] Besides, ketamine attenuates the fentanyl-induced reduction in minute ventilation and suppresses fentanyl-induced cough.[2,3] Whereas, dexmedetomidine has gained popularity as a preferred medication for conscious sedation.[4] It also has anxiolytic, amnestic, analgesic, as well as antisialogogue properties.[5] Dexmedetomidine has a respiratory sparing effect even when administered in large doses.[6,7]

Thus, we hypothesized that better intubating conditions and hemodynamic stability will be achieved with dexmedetomidine as compared to fentanyl with ketamine. This study was carried out with the primary objective to compare the AFOI conditions and with the secondary objective to compare the hemodynamic parameters and level of recall between the two groups.

Methods

After approval from the Institutional Ethical Committee (EC/29/09/16/05), this randomized, double-blind study was planned, and written informed consent was obtained from all the patients. The study was carried out at our institute for over one year. Block randomization was performed using the opaque sealed envelope technique to get an equal number of patients in each group. All the patients included gave consent for the present study, and there was no dropout. Both patients and the anesthesiologist assigned for data collection were kept blinded throughout the study. Different anesthesiologists were assigned for performing sedation and AFOI. For blinding, patients of both the groups were connected to intravenous (IV) infusion, group FK patients received 0.9% normal saline after receiving study drugs (IV fentanyl with ketamine), and group DX patients received dexmedetomidine infusion as per the recommended dose.

Based on the previous literature,[8] taking a power of 90% and α error of 0.05 for this study, the minimum sample size was calculated to be twelve per group with a 20% reduction in endoscopy time. So finally, 30 patients were included in each group to meet the minimum number of normal distribution. After randomization, 60 patients of either sex between 18–55 years of age, belonging to the American Society of Anesthesiologists (ASA) physical status I–II with an anticipated difficult airway (Mallampati grade 3 and 4 with mouth opening less than 5 cm) planned for elective surgery enrolled for the study. Exclusion criteria were patient's refusal to consent, a nasal mass, coagulation disorder, allergy to study medication, uncontrolled hypertension, pregnancy, ischemic heart disease, hepatic or renal disorders, and history of recent nasopharyngeal surgery.

Enrolled patients were randomly allocated into two groups with 30 patients each. Group FK: patients received IV fentanyl 2 $\mu g.kg^{-1}$ and IV ketamine 0.25 $mg.kg^{-1}$ with an additional equivalent dose to achieve a Ramsay Sedation Scale (RSS) score of ≥ 2.[9] Group DX: patients received IV dexmedetomidine 1 $\mu g.kg^{-1}$ over 10 minutes bolus followed by an infusion of 0.2 to 0.7 $\mu g.kg^{-1}.hour^{-1}$ to achieve an RSS score of ≥ 2.[9]

Ramsay Sedation Scale (RSS) was used to assess the awake levels: 1) patient anxious and agitated, or restless, or both, 2) patient cooperative, orientated, and tranquil, 3) the patient responds to commands only, 4) a brisk response, 5) a sluggish response, and 6) no response.[9]

Patients were shifted to the operation room (OR) after confirming nil per oral status. Standard ASA monitors like pulse oximetry, noninvasive blood pressure (NIBP), electrocardiogram (ECG), and temperature probe were attached. IV access secured with 18G cannula and ringer lactate solution infused. Preoperatively nasal patency test carried out using cotton and nostril with better patency was preferred. Xylometazoline 0.1 % (as a nasal decongestant) two drops in each nostril instilled 15 minutes before the start of the procedure. The patients received topical anesthesia with 5 mL of 4% lignocaine as nebulization for about 10–15 minutes. All the patients were premedicated with IV glycopyrrolate 0.2 mg 10 minutes before the planned procedure and with ondansetron 4 mg. Study drugs were administered to the patients as per group allocation. All the patients were intubated awake using a fiberoptic bronchoscope (IPX7 S/N 05148). The same anesthesiologist performed the AFOI for all the patients. After the successful passage of the appropriate-sized endotracheal tube (ETT) through the vocal cord, the tube position was confirmed with capnography and bilateral symmetrical air entry on auscultation. General anesthesia was induced using IV propofol 2 $mg.kg^{-1}$

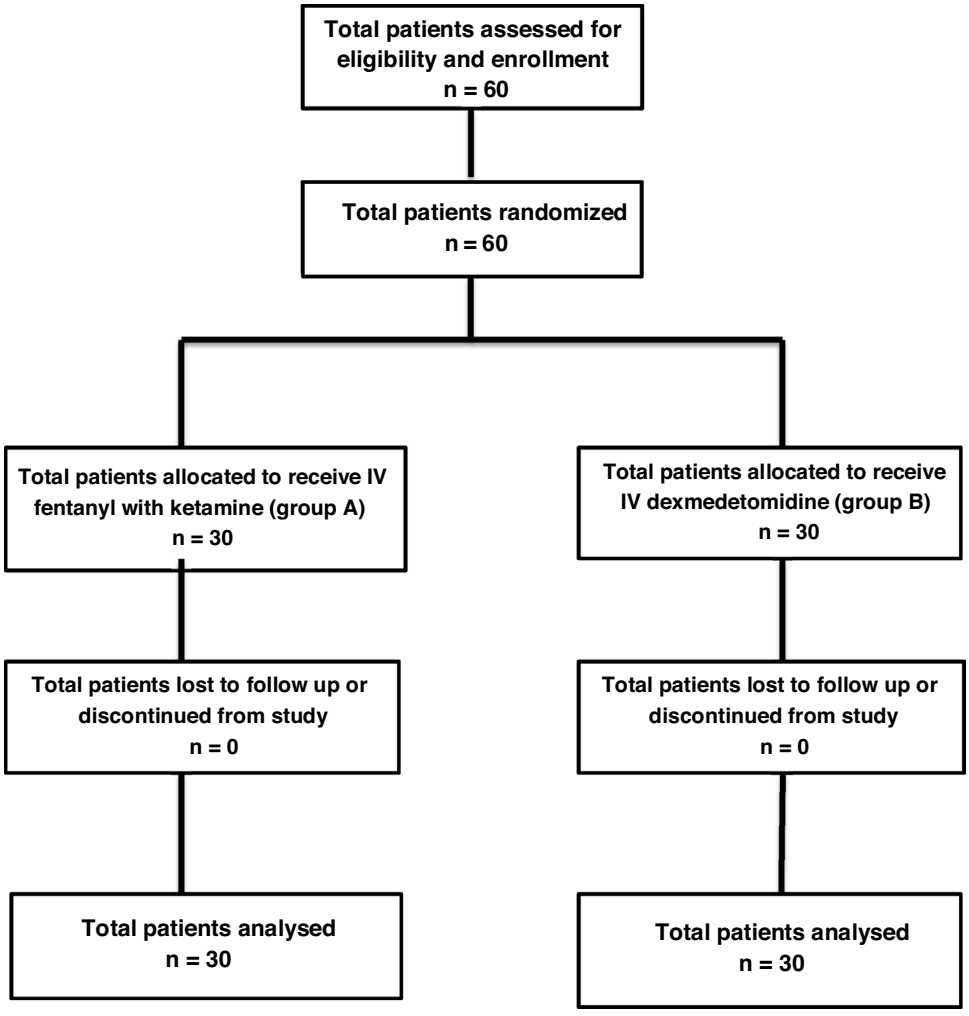

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

and vecuronium bromide 0.1 mg.kg^{-1}, and maintained with isoflurane, 50:50 of oxygen: nitrous oxide, and intermittent IV vecuronium bromide as per requirement. The volume-controlled mode was used for mechanical ventilation and end-tidal carbon dioxide ($ETCO_2$) was maintained between 35 and 40 mmHg.

Hemodynamic parameters like heart rate (HR), mean blood pressure (MBP), respiratory rate (RR), oxygen saturation (SpO_2), and $ETCO_2$ were recorded at baseline. Values were recorded as the zero-minute score after sedating the patient to a RSS score of ≥ 2, then every one-minute interval until completion of the AFOI procedure and successful placement of the ETT. The endoscopy time (from the insertion of fiberscope into the nostril to the visualization of carina) was recorded in minutes. The intubation time (from the insertion of ETT into the nose to confirmation of intubation with capnography) was recorded in seconds. The ease of placement of fiberoptic scope and the ETT assessed using a scale of 1 to 4. It was recorded as the endoscopist satisfaction score (1, excellent; 2, good; 3, fair; 4, poor).[10] The patient's reaction to the placement of the fiberoptic scope and the endotracheal tube was assessed on a scale of 1 to 5 and was recorded as the patient discomfort score (1, no reaction; 2, slight grimacing; 3, severe grimacing; 4, verbal objection; 5, defensive movement of head, hands, or feet).[8] Level of recall of event was recorded after 24 hours during the postoperative visit on a scale of 1 to 4 (1, memory of preanesthetic preparation; 2, memory of topical anesthesia; 3, memory of endoscopy; 4, memory of intubation).[11] In the case of > 3 intubation attempts or SpO_2 < 92% during the procedure, the AFOI was discontinued, and conventional laryngoscopy was performed. Tracheostomy was kept as an alternative for failed intubation attempts.[12]

All 60 patients were assessed for eligibility, enrolled for the study, and underwent randomization. Total patients allocated to receive study drugs were thirty for each group, none of the patients were lost to follow up or discontinued from the study. All the included patients were analyzed (Figure 1). Statistical analysis of the data collected performed using SPSS 16. The normality of data distribution was checked by the Shapiro-Wilks test. Student's *t*-test was used for comparing both the groups. At the same time, Chi-square and non-parametric Mann-Whitney U test were applied to analyze the discrete or categorical variables. The obtained results of continuous variables were expressed as mean (standard deviation [SD]) and categorical values in

Table 1 Demographic characteristics and ASA physical status.

Parameters	Group FK (n = 30)	Group DX (n = 30)	*p*-value
Age (years)	31.2 (13.7)	28.6 (15.9)	0.511
Gender (male/female)	13/17	8/22	0.176
Weight (kg)	57.1 (6.3)	59.9 (6.4)	0.074
ASA class (I/II)	18/12	24/6	0.091

n, number; ASA, American Society of Anesthesiologists.
Data expressed as mean (standard deviation) or as a number.
Using Unpaired *t*-test for age and weight, Chi-Square test for gender and ASA class.

Table 2 Awake fiberoptic intubation parameters among groups.

AFOI Parameters	Group FK (n = 30)	Group DX (n = 30)	*p*-value
Endoscopy time (minutes)	3.5 (1.1)	2.7 (0.8)	0.001[a]
Intubation time (seconds)	39.2 (10.5)	38.0 (11.2)	0.538
First end tidal CO_2 after intubation	41.2 (4.3)	39.3 (2.7)	0.015[a]

n, number; AFOI, awake fiberoptic intubation.
Data are expressed as the mean (standard deviation).
Using Unpaired *t*-test.
Endoscopy time (from the insertion of fiberscope into the nostril to the visualization of carina).
Intubation time (from the insertion of endotracheal tube into the nose to confirmation of intubation with capnography).
[a] Significant ($p < 0.05$).

percentage (%). The values obtained were dichotomized for endoscopist satisfaction score as good satisfaction score (1 and 2) and poor satisfaction score (3 and 4), similarly for patient discomfort score as some discomfort (1 and 2), and considerable discomfort (3, 4, and 5). A *p*-value of less than 0.05 was considered to be significant.

Results

The demographic variables and ASA physical status were comparable ($p > 0.05$) between the two groups (Table 1). All the patients underwent successful AFOI in a single attempt. There was a significant difference in endoscopy time between the two groups ($p < 0.05$), which was more in group FK (3.45 $\pm$ 1.02 minutes) compared to group DX (2.70 $\pm$ 0.80 minutes) (Table 2). The intubation time was similar between both the groups ($p > 0.05$). The first $ETCO_2$ value after tracheal intubation was significantly higher in group FK compared to group DX (41.20 $\pm$ 4.25 mmHg vs. 39.26 $\pm$ 2.72 mmHg) (Table 2). Endoscopists experienced a good satisfaction score for 22 versus 28 patients and poor satisfaction scores for 8 versus 2 patients among groups FK and DX, respectively. So, the endoscopist satisfaction score was significantly better in group DX. Patient discomfort score was comparable between both groups. Among the group FK patients, 24 experienced slight or no discomfort, and 6 had considerable or severe discomfort, similarly among the patients of group DX, 29 experienced slight or no discomfort, and one had significant or severe discomfort (Table 3). There was no difference in recall or awareness among the patients of both the groups during the AFOI procedure ($p > 0.05$) (Table 3).

There was a smaller variation in HR and MBP from baseline with dexmedetomidine compared to fentanyl with ketamine combination. Statistically, significant intergroup differences were observed in HR and MBP from the starting of the AFOI procedure and 5 minutes thereafter, which was significantly higher in group FK compared to group DX ($p < 0.05$) (Table 4).

Patients of both groups maintained arterial oxygen saturation within the satisfactory level (97% to 99%) during the entire procedure of AFOI, and changes were found statistically insignificant (Table 4). Changes in RR of both groups were comparable throughout the procedure. There were no hemodynamic complications like bradycardia, tachycardia, hypotension, hypertension, arrhythmia, desaturation throughout the procedure in both the groups.

Discussion

This study compared the effectiveness of fentanyl with ketamine versus dexmedetomidine in achieving a favorable condition for AFOI. The role of fentanyl as an effective analgesic and anxiolytic drug is well known, but it causes respiratory depression, which is not desirable for AFOI. Adding a low dose of ketamine to fentanyl enhances the hemodynamic stability. However, fentanyl with ketamine causes a simultaneous increase in oxygen consumption.[11] Dexmedetomidine is a selective α_2 agonist, causes sedation without loss of consciousness or respiratory depression. In this study, $ETCO_2$ value was recorded for confirmation of endotracheal intubation as well as to assess the respiratory depressant effect of the study drugs.[13] The first $ETCO_2$ was significantly higher in group FK compared to group DX, indicating that fentanyl associated with ketamine may produce more respiratory depression than dexmedetomidine. This study result is in agreement with the trial conducted by Midth et al.[2]

The endoscopic procedures are commonly used for both screening as well as therapeutic purposes. For a successful

Table 3 Endoscopist satisfaction score, patient discomfort score and level of recall of event among groups.

Parameters		Group FK (n = 30)	Group DX (n = 30)	*p*-value
Endoscopist satisfaction score	1	5 (17%)	4 (13%)	0.013[a]
	2	17 (57%)	24 (80%)	
	3	8 (26%)	2 (7%)	
	4	0	0	
Patient discomfort score	1	2 (7%)	7 (24%)	0.249
	2	22 (73%)	22 (73%)	
	3	4 (13%)	1 (3%)	
	4	2 (7%)	0	
	5	0	0	
Level of recall of event	1	23 (77%)	24 (80%)	1.0
	2	5 (17%)	5 (17%)	
	3	2 (6%)	1 (3%)	
	4	0	0	

n, number.
Data expressed as number (percentage).
Using Mann-Whitney U test.
Endoscopist satisfaction score (1, excellent; 2, good; 3, fair; 4, poor).
Patient discomfort score (1, no reaction; 2, slight grimacing; 3, severe grimacing; 4, verbal objection; 5, defensive movement of head, hands, or feet).
Level of recall of event (memory of pre-anesthetic preparation-1, memory of topical anesthesia-2, memory of endoscopy-3, memory of intubation-4).
[a] Significant ($p < 0.05$).

Table 4 Hemodynamic parameters.

Time (min)	Heart rate (min^{-1})			Mean blood pressure (mmHg)			SpO_2 (%)		
	Group FK	Group DX	*p*-value	Group FK	Group DX	*p*-value	Group FK	Group DX	*p*-value
Baseline	85.8 (12.5)	84.7 (12.9)	0.859	89.4 (9.2)	90.9 (10.8)	0.717	99.0 (0.8)	99.2 (0.9)	0.086
0	78.6 (9.4)	73.8 (9.0)	<0.001[a]	87.8 (7.7)	81.3 (10.3)	0.003[a]	98.8 (0.7)	98.9 (0.8)	0.66
1	84.2 (8.0)	75.9 (8.7)	<0.001[a]	91.2 (6.9)	81.6 (10.2)	0.001[a]	98.6 (0.7)	98.6 (0.7)	0.769
2	88.3 (8.8)	76.5 (7.8)	<0.001[a]	93.5 (7.1)	82.0 (10.3)	<0.001[a]	98.5 (0.6)	98.5 (0.6)	0.713
3	92.1 (10.4)	65.1 (9.3)	<0.001[a]	96.0 (5.8)	79.3 (10.3)	0.014[a]	98.3 (0.6)	98.5 (0.7)	0.466
4	94.4 (9.6)	75 (6.8)	<0.001[a]	98.7 (5.7)	84.3 (6.6)	0.02[a]	98.3 (0.6)	98.4 (0.7)	0.523
5	106.4 (8.9)	73.5 (2.1)	<0.001[a]	101.2 (4.6)	93.0 (9.8)	0.001[a]	98.3 (0.5)	98.3 (0.7)	0.635

Data are expressed as mean (standard deviation).
Using Unpaired *t*-test.
SpO_2, oxygen saturation.
[a] Significant ($p < 0.05$).

endoscopic procedure, patient and endoscopist compliance plays an important role. In this study, the quality of the AFOI was assessed using patient discomfort score and endoscopist satisfaction score. Although the patient discomfort score was comparable between both groups, patients who received dexmedetomidine were more comfortable (slight or no discomfort versus considerable or severe discomfort: 24 vs. 6 in group FK compared to 29 vs. 1 in group DX). This effect might be because of the better ability of dexmedetomidine to sedate the patients and relieving their anxiety. The sedative effect of dexmedetomidine is due to presynaptic activation of α_2 adrenoreceptor in the locus coeruleus that inhibits norepinephrine release.[14] This finding is not consistent with the study conducted by Liu et al.,[15] where the effect of remifentanil or dexmedetomidine compared during awake fiberoptic orotracheal intubation and the comfort scores and airway events during intubation did not significantly differ between the two groups. Endoscopist satisfaction score as well as endoscopy time was better in the dexmedetomidine group due to better patient cooperation and the antisialagogue effect of dexmedetomidine. This study result is in agreement with the study conducted by Sergio et al.,[16] and Abdelmalak et al.[17]

Changes in the HR and MBP were significantly higher in patients receiving fentanyl with ketamine from the start of the procedure until completion of AFOI, unlike the study conducted by Rajan et al.,[18] which shows comparable hemodynamics. So, there are smaller variations in HR and MBP from baseline with dexmedetomidine than fentanyl with ketamine combination. This finding was consistent with another study conducted by Hu et al., comparing the effects of remifentanil and dexmedetomidine during AFOI.[19] Hemo-

dynamic stability with the use of dexmedetomidine was also favoured by another study conducted by Patel et al.[20] Throughout the procedure, RR and SpO_2 were comparable.

However, this study has certain limitations, like single center trial, small sample size, problems in maintaining blinding, and variation in tolerance to fiberoptic intubation among patients. In future, multicentric trials involving larger sample size could be carried out to validate the findings of this study.

In summary, our study has demonstrated that, although both strategies seem to be safe and effective, dexmedetomidine provides better intubating conditions with smaller hemodynamic variation compared to fentanyl with ketamine for awake fiberoptic intubation in patients with a difficult airway.

Conflicts of interest

The authors declare no conflicts of interest.

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