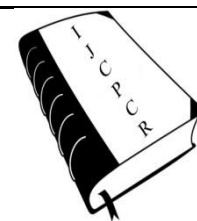




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A STUDY OF COMPARISON BETWEEN DEXMEDETOMIDINE- MIDAZOLAM AND FENTANYL-MIDAZOLAM ON AWAKE FIBEROPTIC INTUBATION.

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ABSTRACT

Awake fiberoptic intubation (AFOI) is usually performed in the management of the anticipated difficult airway. The aim of this study was to evaluate the feasibility of dexmedetomidine with midazolam (DM) and fentanyl with midazolam (FM) for sedation for awake fiberoptic nasotracheal intubation. Fifty patients with restricted mouth opening scheduled for AFOI were randomly assigned to two groups (n = 25 per group). All subjects received midazolam 0.02 mg/kg as premedication and airway topical anesthesia with a modified “spray as you go” technique. Group DM received dexmedetomidine at a loading dose of 0.5 µg/kg over 10 min followed by a continuous infusion of 0.25 µg/kg/h, whereas Group FM received fentanyl at a loading dose of 2 µg/kg over 10 min followed by a continuous infusion of 1 µg/kg/h. As necessary, since the end of the administration of the loading dose of the study drug, an additional dose of midazolam 0.5 mg at 2 min intervals was given to achieve a modified Observers’ Assessment of Alertness/Sedation of 2–3. The quality of intubation conditions and adverse events were observed. The scores of ease of the AFOI procedure, patient’s reaction during AFOI, coughing severity, tolerance after intubation, recall of the procedure and discomfort during the procedure were comparable in both groups (z=0.572, 0.664, 1.297, 0.467, 0.895, and 0.188, respectively, P > 0.05). Hypoxic episodes similarly occurred in the two groups, but the first partial pressure of end tidal CO₂ after intubation was higher in Group FM than that in Group DM (45.2 ± 4.2 mmHg vs. 42.2 ± 4.3 mmHg, t = 2.495, P < 0.05). Both dexmedetomidine and fentanyl are effective as an adjuvant for AFOI under airway topical anesthesia combined with midazolam sedation, but respiratory depression is a potential risk in the fentanyl regimen.

Key words: Awake Fiberoptic Intubation; Conscious Sedation; Dexmedetomidine; Midazolam; fentanyl

INTRODUCTION

Awake fiberoptic intubation (AFOI) is usually performed in the management of the anticipated difficult airway. Adequate sedation with effective airway topical anesthesia for AFOI is paramount to improve intolerance, alleviate discomfort, and achieve successful intubation. However, it is usually difficult to achieve all the requirements for AFOI using a single drug or technique. Benzodiazepines combined with opioids are currently used

for sedation for AFOI. Unfortunately, this combination of drugs has the potential to cause respiratory depression. Contrary to opioids, dexmedetomidine has not been associated with respiratory depression when used alone or combined with midazolam.

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The effectiveness of dexmedetomidine for AFOI has been evaluated in many studies with favourable results.[29] In this study, our aim was to compare the feasibility of dexmedetomidine with midazolam (DM) and fentanyl with midazolam (FM) for conscious sedation for awake fiberoptic nasotracheal intubation under airway topical anesthesia with a modified “spray as you go” technique in patients undergoing oro-maxillofacial surgery.

Methods

Patients

This comparison study was approved by the Ethical Committee of Institute, Sri Lakshmi Narayana Institute of Medical Sciences and written informed consent was obtained from each patient. Fifty patients with American Society of Anesthesiologists (ASA) classifications of I-II were enrolled for elective awake fiberoptic nasotracheal intubation following diagnosis maxillofacial fracture with limited mouth opening. Exclusion criteria included: Pregnant or lactating women, age <18 years or >60 years, cardiopulmonary disease, heart rate (HR) <50 beats/min, systolic blood pressure (SBP) <90 mmHg, allergy to the drugs involved in the study, inability to communicate effectively, patient refusal, history of drug or alcohol abuse, and patients on long term opioids or sedative medication.

Study design

These patients were randomly assigned by computer generated randomization schedule into Group DM or Group FM. Two experienced consultant anaesthetists clinically managed the trial: One mainly responsible for performing the procedure of AFOI and the other mainly for observation and data collection. Study drug was prepared as 200 µg (4 ml) of dexmedetomidine in 46 ml of 0.9% saline or 800 µg (16 ml) of fentanyl in 34 ml of 0.9% saline to 50 ml syringes and administered by a resident anaesthetist according to group allocation and the patient's weight in kilograms. Bronchoscopy was performed by a single anesthesiologist in all patients. The anesthesiologist who performed AFOI and who recorded data were all blinded to the group identities.

Anesthesia and awake fiberoptic intubation procedure

On arrival in the anesthetic room, standard monitoring was established including non-invasive blood pressure, pulse oximetry, and electrocardiography. Patients were asked to breathe through each nostril to assess patency. The nostril with the greatest patency was prepared using cotton pledges soaked in 4% lignocaine 5 ml for 10 min. Once an intravenous cannula was inserted, midazolam 0.02 mg/kg as premedication were given intravenously and the infusion of the study drug was started. All patients received the same drug delivery mode, with which their respective drug was infused at a loading dose of 0.125 ml/kg over 10 min followed by a continuous infusion of

0.0625 ml·kg⁻¹·h⁻¹ via a pressure driven syringe pump. Group DM received dexmedetomidine at a loading dose of 0.5 µg/kg followed by a continuous infusion of 0.25 µg·kg⁻¹·h⁻¹, while Group FM received fentanyl at a loading dose of 2 µg/kg followed by a continuous infusion of 1 µg·kg⁻¹·h⁻¹. Crystalloid fluids (5–10 ml·kg⁻¹·h⁻¹) were administered during the infusion of the study drug.

The level of sedation was assessed by the endoscopic anaesthetist using modified Observers' Assessment of Alertness/Sedation scale (OAA/S, 1 = appropriate verbal response to patient's name, 2 = lethargic response, 3 = response only after name is spoken loudly and/or repeatedly, 4 = response after mild prodding or shaking, 5 = response after painful stimuli)[10] and BIS once per minute.

At the end of infusion of the loading dose, any patient with a modified OAA/S = 1 was given an additional midazolam 0.5 mg at 2 min intervals until a modified OAA/S of 2–3. After adequate sedation was achieved, a fiberoptic scope loaded with a 7.5 mm reinforced tracheal tube for male patients or a 7.0 mm tube for females was inserted through the prepared nostril into the hypopharynx. Airway topical anesthesia was performed with a modified “spray as you go” technique using 2% lidocaine sprayed onto the airway structures via the working channel of the fiberoptic scope. A spray of 2 ml of lidocaine at 15 sec intervals was given until the tip of the fiberoptic scope can be advanced to the next airway structure, and the epiglottis, glottis, and carina were identified. Once the position of the endoscope in the trachea was confirmed, the tracheal tube was positioned approximately 3 cm above the carina and secured. Blood pressure, pulse, oxygen saturation, and respiratory rate were recorded every 3 min from starting the infusion of the study drug until the fiberoptic scope was introduced through the nose. Thereafter, vital signs were recorded every minute until the completion of the AFOI. Hypotension was defined as SBP <80 mmHg, diastolic blood pressure (DBP) <50 mmHg, or a SBP decrease to ≥30% below baseline. Hypertension was defined as SBP >180 mmHg, DBP >100 mmHg, or a SBP increase to ≥30% above baseline. Bradycardia was defined as HR <50 beats/min or a decrease to ≥30% below baseline. Tachycardia was defined as HR >120 beats/min or an increase to ≥30% above baseline. Respiratory depression was defined as respiratory rate <8 breaths/min or a decrease to ≥25% below baseline. Hypoxia was defined as pulse oxygen saturation (SpO₂) <92%. If the modified OAA/S score was 5, infusion of the study drug was discontinued. If a hypoxic episode occurred without an improvement via instructing to make deep breathes, infusion of the study drug was discontinued and naloxone 50 µg was intravenously administered. The patients receiving naloxone were excluded from the research.

Measuring variables

The primary outcome measures were the scores observed during endoscopy, intubation, and postintubation. The endoscopic anesthetist assessed the ease of placement of the fiberoptic scope and endotracheal tube on a scale of 1–3 (1 = easy, 2 = moderate, and 3 = difficult).[3]The observing anesthetist assessed patient reaction to placement of the fiberoptic scope and the tracheal tube on a 5-point scale (1 = no reaction; 2 = slight grimacing;3 = severe grimacing; 4 = verbal objection; and5 = defensive movement of head, hands, or feet).[11]Cough severity was rated on a 4-point scale (1 = none,2 = slight, 3 = moderate, 4 = severe). Coughing wasconsidered slight if no more than 2 coughs in sequenceoccurred, moderate if 3–5 coughs in sequence occurredand severe if more than 5 coughs in sequence occurred.[12]After intubation, the observing anesthetist assessed patient tolerance to the endotracheal tube in the trachea via slow inflation of the endotracheal tube cuff on a 3-pointscale (1 = cooperative, 2 = restless/minimal resistance,3 = severe resistance/general anesthesia requiredimmediately).[4] The intubation time (from inserting thefiberoptic scope into the nostril to confirmation of tracheal intubation with capnography) and the number of attempts to place the fiberoptic scope and the endotracheal tube were recorded. Each patient was asked by one of the two consultant anesthetists 24 h after surgery to grade his/her recall of the procedure (1 = none, 2 = partial, 3 = full) andthe discomfort during the procedure (1 = none, 2 = mild,3 = moderate, 4 = severe).[13]Other parameters assessed in relation to the AFOI procedure included: Airway patency on a 3-point scale (1 = patentairway, 2 = airway obstruction relieved by neck extension,3 = airway obstruction requiring jaw retraction),[4] additionaldosage of midazolam, lidocaine dosage used, the first partial pressure of end-tidal CO2 (PETCO2) after successful intubation (that is, the value of end-tidal CO2 triggered bythe first respiratory cycle with establishment of respiratorycircuit system), any hypoxic episode, any hypotensive or hypertensive episode and any arrhythmic episode.

Statistical analysis

According to a power calculation, 25 patients per groupwere at least required to demonstrate a 30% difference in the intubation sores for a power of 0.8 and a type one error of 0.05. Numerical data were expressed as mean with a standard deviation and categorical data were put into tables. Statistical analyses were carried out using the statistical package for the social sciences 16.0 statistical software packages. Numerical data were compared between two groups using independent *t*-test and

within the same group using paired *t*-test. Categorical data were compared between two groups using Chi-square test. All analysis was two tailed and *P* < 0.05 was considered statistically significant.

Results

Patient’s characteristics

No patients were excluded in this study. There were nosignificant differences between the groups with respectto gender, age, height, weight, body mass index, ASA,inter-incisor distance and Mallampati classification(*P* > 0.05) [Table 1].

Quality of awake fiberoptic intubation procedure

The scores of ease of AFOI, patient’s reaction to the AFOI procedure, coughing severity and patient’s tolerance after intubation were comparable in both groups (*P* > 0.05).The number of attempts and the intubation time weresimilar between the groups (*P* > 0.05). There wasno difference in recall or awareness of the AFOIprocedure and patient’s discomfort score between thegroups (*P* > 0.05) [Table 2].

Data related to anesthesia

The score of the modified OAA/S was similar at the end of infusion of the loading dose between the groups (*P* > 0.05),but compared to Group FM, the level of sedation was deeper at immediately before endoscopy, immediately after intubationand 2 min after intubation in Group DM (*z* = 2.117, 2.395,and 2.380, respectively, *P* < 0.05). The score of airwaypatency, the additional dosage of midazolam, and the dosageof lidocaine used were similar in both groups (*P* > 0.05)[Table 3].

Adverse events and first partial pressure of end-tidal CO2 after intubation

The incidence of adverse events including hypertension,hypotension, tachycardia, bradycardia and hypoxia were comparable between the groups, but the first PETCO2after intubation was higher in Group FM than that in Group DM (*t* = 2.495, *P* < 0.05) [Table 4].

Changes in bispectral index values and hemodynamics

BIS score, mean arterial pressure (MAP) andHR decreased continually before endoscopy and increasedimmediately after intubation in both groups. At the time points of the end of infusion of the loading dose (T1),immediately before endoscopy (T2), immediately afterintubation (T3) and 2 min after intubation (T4), the BIS index was lower in Group DM than that in Group FM (*P* < 0.05),but there were no differences in MAP and HR between the two groups.

Table 1: Characteristics of patients allocated in Group DM and Group FM

Characteristics	Group DM (n = 25)	Group FM (n = 25)	Statistical value	<i>P</i> Value
Males/females	21/4	19/6	0.125*	0.724
Age, years	37.9 ± 11.1	36.7 ± 11.5	0.375†	0.709

Weight, kg	67.2 ± 11.2	65.7 ± 10.7	0.484†	0.630
Height, cm	166.8 ± 7.8	167.7 ± 8.1	0.400†	0.691
ASA class, I/II	19/6	18/7	0.319‡	0.750
Inter-incisor distance, mm	13.5 ± 7.8	13.1 ± 8.2	0.177†	0.860
Mallampati airway class, 3/4	20/5	18/7	0.656‡	0.512

Data are n or mean ± SD. DM: Dexmedetomidine with midazolam; FM: Fentanyl with midazolam; ASA: American Society of Anesthesiologists *: χ^2 value, †: t value, ‡: z value.

Table 2: Data related to the AFOI procedure in Group DM and Group FM

Category	Group DM (n = 25)	Group FM (n = 25)	Statistical value	P Value
Ease of AFOI, 1/2/3	16/8/1	18/6/1	0.572*	0.568
Patient's reaction to the AFOI procedure, 1/2/3/4/5	15/8/2/0/0	17/6/2/0/0	0.664*	0.519
Cough severity, 1/2/3/4	15/5/5/0	19/4/2/0	1.297*	0.195
Patient's tolerance after intubation, 1/2/3	22/3/0	23/2/0	0.467*	0.641
Intubation time, min, mean ± SD	4.6 ± 1.4	4.2 ± 1.2	1.085†	0.283
Recall score, 1/2/3	23/2/0	21/3/1	0.895*	0.371
Discomfort score, 1/2/3/4	16/9/0/0	17/7/1/0	0.188*	0.851

DM: Dexmedetomidine with midazolam; FM: Fentanyl with midazolam; AFOI: Awake fiberoptic intubation. *: z value, †: t value.

Table 3: Anaesthetic data in Group DM and Group FM

Category	Group DM (n = 25)	Group FM (n = 25)	Statistical value	P Value
Modified OAA/S; 1 (alert)/2/3/4/5 (asleep)	8/7/8/2/0	10/10/5/0/0	1.436*	0.151
End of infusion of the loading dose				
Immediately before endoscopy	0/11/12/2/0	0/18/7/0/0	2.117*	0.034
Immediately after intubation	0/11/12/2/0	0/19/6/0/0	2.395*	0.017
2 min after intubation	0/10/13/2/0	0/18/7/0/0	2.380*	0.017
Airway patency, 1/2/3	24/1/0	22/3/0	1.032*	0.302
Lidocaine dosage, mg, mean ± SD	194.4 ± 55.8	200.8 ± 59.9	0.391†	0.698

DM: Dexmedetomidine with midazolam; FM: Fentanyl with midazolam; OAA/S: Observers' Assessment of Alertness/Sedation. *: z value, †: t value

Table 4: Adverse events and first PETCO2 after intubation in Group DM and Group FM

Category	Group DM (n = 25)	Group FM (n = 25)	Statistical value	P Value
Hypertension, n (%)	2 (8)	3 (12)	0.000*	1.000
Hypotension, n (%)	0 (0)	0 (0)	0.000*	1.000
Tachycardia, n (%)	0 (0)	1 (4)	0.000*	1.000
Bradycardia, n (%)	2 (8)	0 (0)	0.521*	0.470
Hypoxia, n (%)	2 (8)	3 (12)	0.000*	1.000
First PETCO2 after intubation; mmHg	42.2 ± 4.3	45.2 ± 4.2	2.495†	0.016

PETCO2: Partial pressure of end-tidal CO2; DM: Dexmedetomidine with midazolam; FM: Fentanyl with midazolam. *: χ^2 value, †: t value

Discussion

This study showed that both DM regimen and FM regimen were effective as an adjuvant for AFOI under airway topical anesthesia. The two regimens were comparable in achieving desired sedation, satisfactory intubation conditions, stable hemodynamics, and low-level recall. Optimal conditions for AFOI require sufficient comfort, adequate cooperation, stable hemodynamics and amnesia without respiratory depression. Single drug or technique currently in use is difficult to meet all the requirements for AFOI. In this study, the patients receiving DM had intubation conditions, hemodynamic profiles and recall of the AFOI procedure equal to the patients receiving FM. The additional dosage of midazolam required to achieve adequate sedation and the dosage of lidocaine consumed to perform airway topical anesthesia were similar in both groups. Nonetheless, we found while the modified OAA/S score was comparable at the end of infusion of the loading dose in both groups, the BIS scores were significantly lower in Group DM than those in Group FM, which similar with the findings of Kasuya *et al.*[14] and Haenggi *et al.*,[15] who reported that at comparable OAA/S or Ramsay scores, BIS values were significantly less with dexmedetomidine than those with propofol or midazolam. Some studies have focused on finding the correlation between the BIS and OAA/S score for dexmedetomidine[14,15] and midazolam,[16,17] and a divergence between the BIS and OAA/S scores has been reported.[14,16] A recent study found that the BIS value at which 50% patients lost consciousness was elevated from 63 when propofol used alone to 71 when propofol used together with dexmedetomidine,[18] which indicated that dexmedetomidine enhanced the hypnotic effects of propofol. The hypnotic synergism has been shown between dexmedetomidine and midazolam in two animal trials,[19,20] and to our knowledge, clinical studies have yet to verify this synergism. Therefore, since the impact of dexmedetomidine on BIS is incomprehensible, sedative scales like OAA/S may be more suitable to determine the adequacy of sedation, especially when dexmedetomidine is used with other sedatives. Many agents have been reported to achieve conscious sedation for AFOI. Fentanyl can provide potent analgesia and blunt airway reflexes with minimal amnesic effect. Midazolam can provide sedation and amnesia without analgesic effect. Dexmedetomidine used for AFOI has become more popular because of its sedative, amnesic, analgesic, and anxiolytic effects without respiratory depression. In previous studies[2-9] on administration of dexmedetomidine for AFOI, the loading dose and the maintenance dose ranged from 0.4 to 1.5 $\mu\text{g}/\text{kg}$ over 10 or 15 min and 0–0.7 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$, respectively, but dexmedetomidine 0.4 $\mu\text{g}/\text{kg}$ followed by a continuous infusion of 0.7 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ combined with midazolam 2 mg as premedication produced less sufficiently sedation and analgesia for AFOI compared to remifentanyl.[5] In this study, the loading dose and the

maintenance dose of dexmedetomidine were 0.5 $\mu\text{g}/\text{kg}$ and 0.25 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$. Recall not only affects patients on the assessment of satisfaction to the AFOI procedure but also would put them at a risk of the negative psychological state. The combination of midazolam and other sedative or analgesic agents may be an optimal sedation scheme for AFOI. The incidence of awareness of airway procedure events was reported in 40–56% of patients receiving dexmedetomidine alone,[2,4,6,7] while 16% of patients receiving DM as premedication.[3] In the present study, midazolam 0.02 mg/kg as premedication with additional doses was administered, and the incidences of recall were comparable in both groups: 16% in Group FM which was lower than that of patients receiving fentanyl alone reported by Shen *et al.*,[2] and 8% in Group DM which was similar to that of Bergese *et al.*[3] In addition, Bergese *et al.*[8] described that the incidence of recall was 60.8% in patients receiving midazolam as rescue sedative combined with dexmedetomidine. The results of the above investigations remind us that midazolam causes antegrade, not retrograde, amnesia, and as premedication, helps to decrease the occurrence of recall. Respiratory depression is the adverse event most concerned by anesthetists when the sedative and analgesic agents are selected for AFOI. While there was no indifference with regard to the incidence of respiratory depression and the score of airway patency in both groups, the first PETCO₂ after intubation was higher in patients receiving FM in this study, as shown by Shen *et al.*,[2] who reported that the incidence of respiratory depression was high to 20% and the first PETCO₂ after intubation was (47.1 ± 4.3) mmHg in patients receiving fentanyl alone. The values of the first PETCO₂ after intubation in patients receiving fentanyl alone or with midazolam were approximate to but above normal values, of which the elevation indicated that the potential risk of insufficient ventilation or respiratory depression was still kept with fentanyl sedation. However, the risk of respiratory depression may be minimized by maintaining cooperation to make deep breathing during AFOI.

The “spray-as-you-go” technique is a common fashion to apply local anesthetics to the airway. The classic “spray-as-you-go” technique is that described by Sanchez *et al.*,[24] includes supraglottic spray 2 times at 5-min intervals, glottic spray at 3-min intervals until adequate anesthesia of the vocal cords and tracheal spray once followed by intubation after 5 min, which consumes at least 18 min. The technique was simplified with glottic spray once and tracheal spray once in several studies,[2-4,6] which might be not effective to blunt the gag reflex and the glottic reflex. Therefore, in order to shorten the time of endoscopy and achieve adequate airway anesthesia, the classic technique was modified with 2% lidocaine 2 ml per spray at 15-sec intervals and step by step and nonviolently advancing the tip of the fiberoptic scope to the next airway structure in the present study. The dosage of lidocaine used in our study was similar with that

reported by Xue *et al.*, [25] significantly lower than the safe dose of 9 mg/kg. [26] The intubation time in our study was obviously shorter than that reported by Shen *et al.* [2] Obviously, adequate topical airway anesthesia is beneficial to facilitate AFOI.

Conclusion

In conclusion, the two regimens used in this study provided comparable intubating conditions, patients' tolerance to intubation and lower recall for airway procedure events. However, it is necessary to keep responsive and cooperative in patients receiving fentanyl as an adjuvant to midazolam sedation for AFOI because respiratory depression is still a potential risk.

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