Comparative Evaluation of Midazolam, Dexmedetomidine & Midazolam With Dexmedetomidine For Sedation In Awake Fibreoptic Intubation.

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ABSTRACT

To evaluate the efficacy of dexmedetomidine, midazolam and dexmedetomidine with midazolam for sedation during awake fiberoptic intubation (AFOI) a Randomized, double-blinded study was done including 150 patients undergoing elective surgery. All patients received intravenous (IV) glycopyrrolate 0.2 mg premedication, oxygen by nasal cannula, and topical local anesthetics to the airway. Group A received dexmedetomidine infusion 1 micro/kg over 10 mins and then infusion at 0.5 micro/kg/min, Group B subjects received IV midazolam 0.05 mg/kg with additional similar doses and Group C patients received midazolam 0.02 mg/kg and dexmedetomidine 0.5 micro/kg over 10 mins, then an infusion of dexmedetomidine 0.2 micro/kg/hr. All these drugs were given to achieve Ramsay Sedation Scale (RSS) score of >or= 2. Time taken to reach RSS >or= 2 and time taken for intubation was assessed. The anesthesiologist rated AFOI ease of placement and patients were assessed for discomfort by cough severity score and discomfort score. Group C took least time for intubation, also patients were significantly calmer and more cooperative during AFOI and had fewer adverse reactions to AFOI than did the other group subjects. Low doses of Dexmedetomidine and midazolam when given in combination are more effective than dexmedetomidine or midazolam alone for sedation in AFOI.
INTRODUCTION:
Airway management is a fundamental aspect of anaesthetic practice and of emergency and critical care medicine. Fiberoptic intubation (FOI) has now become a mainstay of difficult airway management. Sedative medications are often administered in patients undergoing awake FOI to ensure patient comfort and to provide adequate anxiolysis while maintaining a patent airway and ensuring adequate ventilation. Midazolam is a benzodiazepine with particularly potent sedative activity but has side effects like nausea, confusion and respiratory depression. Dexmedetomidine is a selective alpha-2-adrenoceptor agonist with properties of sedation, anxiolysis, analgesic sparing and inhibition of salivary secretion with minimal respiratory depression. This study is aimed to evaluate and compare the efficacy of both the drugs Midazolam and Dexmedetomidine alone and their combination for sedation in management of patients undergoing AFOI.

METHODS
The aims and objectives of this study are:
1. To compare the efficacy of intravenous Midazolam, Dexmedetomidine & Midazolam With Dexmedetomidine for sedation in cases of awake Fiberoptic intubation.[Ramsay Sedation Score]
2. To compare the quality of analgesia in all the 3 groups.[Discomfort during intubation (none, facial grimacing, verbal objection, defensive movement of head or prolonged cough via Cough Score)]
3. To compare the ease of intubation.[Time Taken For Intubation i.e. from administration of sedative to the placement of ETT in all the 3 groups]
4. To compare the effect on hemodynamics [Pulse Rate, Spo2, Non Invasive Blood Pressure (MAP), Respiratory rate] in all the 3 groups.
5. Any other complications encountered during the procedure [CVS adverse effect, mainly hypotension and bradycardia or Spo2<90%]

Design- Randomized prospective double blinded study
Setting- The study was conducted in Department of Anaesthesiology and Critical Care, MLB Medical College, Jhansi (UP) in patient posted for elective surgeries.

Patient Selection- Following the approval from the Ethical committee, ASA I and II Patients with normal airway (Thyromental distance > 6.5 cm; MPG grade I and II; > 90° neck movement; no buck teeth; normal BMI 19 – 25 kg/m²) undergoing elective surgeries were included in this study.

Exclusion Criteria-
1) Patient refusal
2) Patients with severe coagulation disorders.
3) Liver disease and kidney diseases.
4) Patients with recent URTI symptoms.
5) Severe hemodynamic instability.
6) Any other comorbid condition.

Sample Size And Allocation- Minimum requirement was calculated to be 38 cases in each group to detect a significant difference in number of patients requiring rescue drug to achieve proper sedation (Ramsay sedation score [RSS] ≥2) between the three groups with a power of 0.8 and type I error of 0.05. To allow for study error and attrition, 50 cases were taken in each group. The cases were then randomly divided via computer based randomization further into Group A; B and C.

Pre-operative visit was conducted on the day before surgery to take a detailed history and for general and systemic examinations. Patients were explained the indication, risks and benefits of Fiberoptic intubation under sedation and cooperation needed. Routine laboratory investigations were carried out. The preparation of patients in each group was standardized as much as possible. After pre-treatment with 0.2 mg IM Glycopyrrolate, each patient was taken to the operating room where standard monitoring like ECG, pulse-oximeter and NIBP cuff were placed. An 18 G iv cannula was secured and Ringer Lactate was started through it. Inj. Ondansetron 4mg iv was given. For nasal intubation, the patient was placed in a semi-recumbent position and 4 mL Lidocaine 4% was administered either via metered-atomization-device (MAD) catheter through the oral cavity and pharynx to reduce gag reflex.

Group A received a loading dose of iv Dexmedetomidine 1 µg/kg bolus infusion followed by an infusion of 0.5 µg/kg/hr until their RSS was ≥ 2. Group B received iv midazolam 0.05 mg/kg with additional doses 0.05 mg/kg until their RSS was ≥ 2. Group C received iv midazolam 0.02 mg/kg followed by Dexmedetomidine 0.5 µg/kg bolus infusion over 15 minutes and then Dexmedetomidine 0.2 µg/kg/h infusion until their RSS was ≥ 2. The groups included 48; 44 and 50 patients respectively as in 8 patients procedure had to be abandoned and GA was induced hence were excluded from statistical analysis.

An experienced consultant anaesthetist, who was certified in advanced airway life support, performed the airway management when the RSS was ≥ 2 for all the study subjects. While one resident performed Fiberoptic intubation, an additional resident controlled the drug
infusion. Anaesthetic data and postoperative follow-ups were documented by a study nurse. Intubation conditions were graded by the consultant anaesthetist who performed the Fiberoptic intubation. The intubating anaesthetist, patients and the study nurse who recorded the details of the procedures were all blinded to the study.

RESULTS
All the three groups were comparable in terms of age, male : female ratio, BMI (Body Mass Index), and thyromental distance. The p value came out to be >0.05 i.e. statistically insignificant. As shown in this bar diagram, the mean time taken to reach RSS > 2 was minimum in the group C i.e. the combination group and when all the three groups were compared by Analysis Of Variance test it was found statistically very significant (p value <0.001).

The bar diagram shows mean time taken for intubation was least in Group C and which when compared to both the groups as shown in the table below was found statistically very significant (p value <0.001). Similar trends were seen in mean arterial pressure also, there was insignificant fall when groups A and B were compared whereas group C showed significant difference in MAP when compared to the other two Groups. (p value <0.05). There was no significant difference in the baseline values of pulse rate in all the three groups but after 5 minutes of sedation till 120 seconds after AFOI fall in pulse rate was very significantly more in group C when compared to Groups A and B (p value <0.001) while the difference between Group A and B was not found statistically significant. (p value > 0.05).

Mean saturation was maintained above 90% during the sedation and AFOI in all the three groups. Although the fall in saturation was seen during intubation as shown in the graph but it was not found significant (p value 0.085).
Discomfort score was graded into 4 i.e. Grade 0 - No discomfort; Grade 1 - Mild discomfort/Facial grimacing; Grade 2 – Moderate discomfort / Verbal objection ; Grade 3 – Severe discomfort / Defensive movement of head, hands or legs 88% (44 out of 50) of the cases in Group C had no discomfort and none of them complained of moderate or severe discomfort whereas 73% (35 out of 48) in group A and only 45% (20 out of 44) in Group B had no discomfort which on comparison was found statistically very significant. (p value < 0.001).
Cough severity was graded according to number of cough in sequence i.e. None or No cough; Slight or < 2 cough in sequence; Moderate or 3-5 cough in sequence; Severe or >5 cough in sequence. None of the patients in Group C whereas 2% (1 out of 48) and 13.6% (6 out of 44) complained of severe cough which when compared statistically was found significant (p value < 0.05). None of the complications like hypotension, hypertension, tachycardia or hypoxia were seen in any of the patients, although 1 patient in Group A had bradycardia which was treated with Atropine 0.6 mg iv but it was not found significant.

DISCUSSION
The demographic data (age, sex, weight, BMI) was comparable in both the groups. Mondal Stook normal airway sample population and excluded MPG grade III and IV and TMD < 6.5 cm in a study similar to ours. In this study also we excluded the patients with difficult airway and included patients with TMD >6.5 cm and MPG grade I & II with normal BMI; > 90° neck movement; no buck teeth and all the groups were comparable (Table no 1). Patients with normal airway only were taken so as to exclude the bias produced by variation in difficulty level in anticipated difficult airway and it would have affected the time taken for intubation. Besides the sample size would have been reduced considerably to evaluate the efficacy of sedation by the study drugs.

Many sedation scores were used in different studies to assess the level of sedation like conscious score; RASS (Richmond agitation sedation score); OAA/S (Observer Assessment Awareness and Sedation Scale). In our study we used RSS (Ramsay Sedation Score) and found that time taken to reach RSS >2 was least [6.4 +- 0.64] in group C i.e. the combination group of midazolam and Dexmedetomidine (Table & Graph no 2) which was comparable with other similar studies.

In our study, time taken for intubation was taken from insertion of bronchoscope till confirmation of tube position by capnography which was minimum in Group C i.e. 3.35 +- 0.92 mins as compared to 6.71 +- 0.96 mins in Group B and 4.41 +- 0.88 mins in Group A. and was statistically highly significant (Table & Graph no 3). Only 2 studies done by Chu et al and Tsai et al involving 70 participants reported on this outcome, both showing no significant difference between the Dexmedetomidine group and the control group. This may probably because the study was done on oral cancer patients i.e. already the patients with difficult airway which might have produced some bias.

Cardiovascular response to Dexmedetomidine bolus has been described as a transient rise in blood pressure and a decrease in heart rate followed by a fall in blood pressure. A slow loading bolus doses ranging from 0.2-0.6µg/kg/hr are recommended for less hemodynamic alterations. Jorden et al observed that high bolus doses of Dexmedetomidine do not always result in hypertension, and Venn et al reported that high doses of Dexmedetomidine may be used safely without changes in hemodynamics when they are infused over 10 minutes. Similar results were found in our study i.e. Group C when Dexmedetomidine was used in low doses provided less change in Mean Arterial Pressure during AFOI as compared to the Groups A & B (Table no 4). Decreases in HR with Dexmedetomidine occur most commonly during a bolus or within 10 minutes of the start of an infusion. The Group C patients in this study had a significant reduction in HR as compared with the Group A & B patients (Table no. 5). This finding could a reflection of less sympathetic discharge in the combination group patients and being pre-treated with midazolam.

Studies conducted by Tsai et al and Chu et al showed no significant difference regarding decrease in oxygen saturation between the Dexmedetomidine group and the control group. In our study also in any of patients never did the saturation dipped below 90%, although fall in saturation...
was noted during intubation in some patients but it wasn’t found significant (Table no 6) Ease of Fiberoptic intubation was assessed via likert scale and significant proportion in Group C had easy AFOI i.e. 84% [42 out of 50] (Graph no 7). Only 1 study comparing Dexmedetomidine with Sufentanil in AFOI had ease of AFOI as secondary outcome but found no significant difference between them. Overall, the Group C patients were more comfortable with the AFOI than the other groups which were measured via discomfort score and cough severity score (Table no 8 and 9). These findings have been in consistence with the study bolus doses ranging from 0.2-0.6µg/kg/hr are recommended for less hemodynamic alterations. Jorden et al observed that high bolus doses of Dexametomidine do not always result in hypertension, and Venn et al reported that high doses of Dexametomidine may be used safely without changes in hemodynamic when they are infused over 10 minutes. Similar results were found in our study i.e. Group C when Dexametomidine was used in low doses provided less change in Mean Arterial Pressure during AFOI as compared to the Groups A& B (Table no 4).

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**CONCLUSION**

We would like to conclude that the combination of Dexmedetomidine with Midazolam is highly effective in producing sedation and optimal conditions for AFOI and as the drug dosages in this group are less therefore the side effects are also reduced .Also this combination alleviates the need for airway blocks which saves the patient from added pain of needle punctures and prolonged action of local anaesthetics leading to post-extubation anaesthetized airway.

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