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RESEARCH ARTICLE

A PROSPECTIVE RANDOMIZED STUDY TO EVALUATE THE ANALGESIC AND SEDATIVE EFFECTS OF FENTANYL AND MIDAZOLAM TO NALBUPHINE AND MIDAZOLAM IN PATIENTS UNDERGOING AWAKE FIBEROPTIC

Dr. Akshat Taneja¹, Dr. Akash Gupta², Dr. Malti Agrawal³, Dr. Upasana Asooja¹ and Dr. Ashok Taneja¹

1. Junior Resident Department of Anaesthesiology, Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh.
2. Assistant Professor Department of Anaesthesiology, Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh.
3. Head of Department of Anesthesiology, Rohilkhand Medical College and Hospital Bareilly, Uttar Pradesh.

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Abstract

Background- Awake nasal or oral flexible fiberoptic intubation (AFOI) is technique of choice in known or anticipated difficult airway . The main aim was to have calm and cooperative patient who can follow verbal commands while maintaining adequate oxygenation . In our study, we compared the analgesic and sedative effects of fentanyl and midazolam with nalbuphine and midazolam in patients undergoing awake fiberoptic intubation more tolerable and comfortable for the patient but also to ensure optimal intubating conditions.¹

Material and Methods- A prospective, randomized comparison study among patients between the age of 18 and 60yrs of either sex, with anticipated difficult airway . We compared the analgesic and sedative effects of fentanyl and midazolam with nalbuphine and midazolam in patients undergoing awake fiberoptic intubation. The primary objectives of our study were to observe the level of sedation, intubation score and OAS score after completion of procedure. The secondary objectives included assessment of patient comfort, intubation time, hemodynamic changes and complications.

Results – We found that comfort score and intubation time were significant lesser in Group which received fentanyl and midazolam than Group which received nalbuphine and midazolam . (p<0.05). The intubation attempt was similar in both groups (P>0.05).

Conclusion- we concluded that both regimens used in this study provided comparable intubating conditions, better sedation and analgesia was observed in group fentanyl for airway procedure events. Our study concluded fentanyl to be the drug of choice for blunting of pressor response in such patients.

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Introduction:-

Awake nasal or oral flexible fiberoptic intubation (AFOI) is the airway management technique of choice in known or anticipated difficult airway, severe cervical stenosis, Chiari malformation, unstable cervical fracture, limited

Corresponding Author:- Dr. Akash Gupta

Address: - Assistant Professor Department of Anaesthesiology, Rohilkhand Medical College and Hospital, Bareilly , Uttar Pradesh.

mouth opening as in temporomandibular disease, mandibularmaxillary fixation, severe facial burn and vertebral artery insufficiency.ⁱⁱ Tracheal intubation is the placement of a flexible plastic tube into the trachea to maintain a patent airway for ventilation. Failure to maintain patent airway is an important cause of anesthesia-related morbidity and mortality, with subsequent failure of oxygenation and ventilation. Fiberoptic intubation is the best, easiest and most successful method for awake intubation without losing control over patient's spontaneous respiration, but it can be associated with intense nociceptive stimulation, especially during passage of the endotracheal tube (ETT). The main aim of awake intubation is to have a calm and cooperative patient who can follow verbal commands while maintaining adequate oxygenation and ventilation, not only to make the procedure more tolerable and comfortable for the patient but also to ensure optimal intubating conditions.ⁱⁱⁱ

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.

Fentanyl is a synthetic pure μ -receptor agonist with shorter time to peak analgesic effect, larger safety margin, minimal respiratory depression at analgesic doses and rapid termination of effect after small bolus doses, and relative cardiovascular stability.^{iv} Compared to fentanyl, sufentanil produces greater and longer-lasting analgesia and less and shorter-lasting respiratory depression^v, but as a single agent for AFOI, it induces a high incidence of recall.^{vi} It may be relatively ideal of the combination of midazolam and fentanyl for AFOI.

Nalbuphine is a semi-synthetic opioid agonist-antagonist analgesic of phenanthrene series. It has a potent analgesic action equivalent to that of morphine on milligram basis. It binds to μ , kappa, and delta receptors. Nalbuphine may partially reverse or block opioid-induced respiratory depression from the μ -agonist analgesic. Nalbuphine, unlike other agonist-antagonist opioids, for example, pentazocine or butorphanol, does not increase systemic blood pressure, pulmonary artery blood pressure, heart rate (HR), or arterial filling pressure. For this reason, nalbuphine may be useful to provide sedation and analgesia in patients with heart disease, for example, during cardiac catheterization.^{vii,viii}

Good topical anaesthesia is essential to obtund the sensory afferent stimuli of the oropharyngeal and laryngotracheal region. Establishing topical anaesthesia before intubation prevents coughing, swallowing, laryngospasm and excessive salivation. Both optimal intubating conditions and patient comfort are necessary while preparing the patient for fiberoptic intubation. An ideal sedative is expected to provide comfort and elicit patient cooperation while maintaining haemodynamic stability and spontaneous ventilation. Drugs used for sedation during awake fiberoptic intubation include fentanyl, midazolam, ketamine, propofol, dexmedetomidine, remifentanyl etc.^{ix,x,xi} Previous studies from Indian population were reported fentanyl provided better sedation and analgesia, obtunded airway reflexes and minimized pressor response to awake fiberoptic intubation and provided better patient comfort than nalbuphine along with traditional sedatives such as propofol¹ and midazolam^{xii} during AFOI.

This study aimed to assure the reliability and validity of the results when applied on different individuals and in a different setup and to strengthen the previous research by finding and correcting the limitations so that the results could be generalized. Moreover, it was to inspire new research counting previous findings from related studies which can add to the body of information supporting the discipline. In our study, we compared the analgesic and sedative effects of fentanyl and midazolam with nalbuphine and midazolam in patients undergoing awake fiberoptic intubation. The primary objectives of our study were to observe the level of sedation, intubation score and OAS score after completion of procedure. The secondary objectives included assessment of patient comfort, intubation time, hemodynamic changes and complications.

Material Method:-

This prospective, randomized comparison study was conducted in department of Anaesthesia and intensive care, Rohilkhand Medical College and Hospital Bareilly after obtaining the approval from Research Ethical Committee of and written informed consent was obtained from each patient.

80 patients posted for facio-maxillary/ head and neck surgeries or patient with anticipated difficult airway were enrolled and patients were randomly assigned according to computer generated random number table

Sample Size

assuming 30% mean difference as significant with alpha level of 0.05 and power at 80%, sample size was calculated to be 33. Anticipating the possible drop out, the required sample size was taken to as 40 per group. The anonymity of the patients was maintained.

Enrolled patients between the age of 18 and 60yrs of either sex, scheduled for elective surgery, all the patients had anticipated difficult airway with either Mallampatti grade II – IV and ASA grade I and II were enrolled in this study. Patients with airway pathologies, had emergency surgeries, bronchial asthma, ASA grade III – IV and any patient with cardiac pathology were excluded from study.

Procedures

Using a computer-generated random number table, the patients were divided into two groups: group N and group F. Five minutes before intubation, group N patients received inj. nalbuphine (0.2 mg/kg) i.v., while group F patients received inj. fentanyl (2 g/kg) i.v. Preanaesthetic check-up was done in every patient including detailed history, clinical examination and necessary investigations. Routine fasting rules were outlined and anti-aspiration prophylaxis was administered to all patients the night before surgery after a thorough pre-anaesthetic evaluation (including complete airway assessment).

Standard monitoring techniques such as electrocardiography, noninvasive blood pressure (NIBP), and pulse oximetry (SpO₂) were used on all patients on the operating table. A ringer lactate infusion was started after the intravenous line is secured. All patients were given an injection (inj.) of glycopyrrolate 0.2 mg intramuscularly (i.m.) 30 minutes before the procedure started, after their baseline blood pressure (BP), heart rate (HR), and oxygen saturation were recorded. Both nostrils were tested for patency, and four drops of xylometazoline nasal drops were instilled in the more patent nostril.

Then, 15 minutes before intubation, an injection of midazolam 0.05 mg/kg was given. Two puffs of 10% lignocaine were sprayed on the posterior pharyngeal wall, with the patient instructed to withhold as much of the 10% lignocaine as possible. The posterior pharyngeal wall was anaesthetized locally as a result of this.

The Observer's Assessment of Alertness/sedation (OAS) score was used to determine the level of sedation at this time. The contralateral nostril was then introduced with a lubricated nasopharyngeal airway of appropriate size.

During the surgery, the breathing circuit was attached to the end of this airway, providing 100 percent oxygen.

Two millilitre (ml) aliquots of 4 percent Lignocaine mixed with 3 ml air was loaded into four separate syringes and were kept ready for injection into the fiberscope's operating channel. A 3.5mm diameter fiberoptic bronchoscope (FOB) with a functional channel for medication instillation was lubricated with aqueous gel and loaded with a polyvinylchloride-coated, cuffed endotracheal tube (ETT) (size 7.5 for females and size 8.0 for males).

Fiberscope was introduced and advanced to the nasopharynx and oropharynx while visualising the structures after 2 percent lignocaine jelly is applied to the prepped nostril. After viewing of the carina, lignocaine 4 percent was sprayed in aliquots of two mL each through the fiberscope's working channel at four levels: epiglottis, supraglottis area, subglottic area, and distal trachea (total lignocaine dose = 320 mg). The anaesthetist waited 30 to 40 seconds after injecting each aliquot before proceeding. The overall dose of lignocaine utilised, however, did not exceed five mg/kg of body weight. The anaesthetist then instructed the helper to move the tube (with lubricated tip) over the fiberscope, which was kept in place by the anaesthetist. To avoid fiberscope dislocation, the carina was always kept in the field of vision. The ETT was placed in place 3-5 cm above the carina and attached to the anaesthetic breathing circuit.

Hemodynamic profile including systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP) and HR at baseline and every 1 min till the end of intubation and every two minutes till ten minutes after the intubation.

The level of sedation using OAS score before starting intubation. Score 5=Appropriate verbal response to patient's name, score 4= Lethargic response, score 3=Response only when name is spoken loudly, score 2=Response after mild shaking, score 1=Response after painful stimuli and score 0=No response.

Vocal cord movement score– this score included observation of vocal cord movement score 1=open, score 2=moving, score 3=closing, score 4=closed.

Cough score (score 1=none, score 2=slight, score 3=moderate, score 4=severe).

Limb movements score 1=no movements, score 2=slight, score 3=moderate, score 4=severe.

Mean intubation score : sum of vocal cord movement score, limb movement score and cough score was used to grade intubating condition of the patient.

Intubation time : from inserting the fiberscope confirmed nasotracheal intubation by appearance of end tidal CO₂ (EtCO₂) curve.

Number of attempts of intubation : maximum 2 attempts of awake fiberoptic nasotracheal intubation was taken, after 1st failed attempt patient was reconciled and 2nd attempt was taken after 5 minutes. On failure of 2 attempts patient was excluded from the study and nasotracheal intubation was done with conventional methods.

Patient tolerance was assessed by comfort score, whose value was the sum of five-point patient comfort score (1=no reaction, 2=slight grimacing, 3=heavy grimacing, 4=verbal objection, 5=defensive movement of head or hands).

Patient satisfaction score was enquired from the patient at the end of surgery in the post-operative recovery room.(1-excellent,2-good,3-reasonable,4-poor)

Statistical Analysis

Analysis was conducted using IBM SPSS statistics (version 20.0). Statistical Analysis is done by using Chi square test; means of 2 continuous normally distributed variables were compared by independent samples, Student's t-test. p value of 0.05 was considered statistically significant.

Observation & Results:-

There were no significant differences between the groups with respect to gender, age, ASA, inter-incisor distance and Mallampati classification ($P > 0.05$) [Table no. 1]. Both mean comfort score and intubation time were significant lesser in Group F than Group N ($p < 0.05$).

The intubation attempt was similar in both groups ($P > 0.05$) [table no. 2]. The scores of ease of AFOI, coughing severity and limb movement were comparable in both groups ($P > 0.05$) [Table no. 3]. The level of sedation in both the groups was assessed by OAS score. 36 (90%) patients in group F had OAS score ≤ 3 while 25 patients (62.5%) in group N had OAS score ≤ 3 . The difference between the two groups is statistically significant ($P=0.022$) [Table no. 4].

Both Heart rate (per minute) and MAP (mmHg) between the two study groups showed significant differences at all the time intervals ($p < 0.05$) except at baseline [fig. 1,2].

The maximum increase in heart rate at the end of intubation was 10.89% in group F & 16.62% in Group N. The mean oxygen saturation values were comparable in both the groups at all intervals of time [fig 3].

Patient satisfaction score was assessed in the recovery room. 50% of the patients in group F showed excellent satisfaction versus 40% patients in group N. 32.5% patients in both the groups showed good satisfaction. While only 15% patients in group F and 20% patients in group N showed reasonable satisfaction. More 7.5% patients had poor response in group N in comparison to 2.5% in group F. Overall the values in both the groups were comparable and non-significant ($P=0.630$) [Fig. 4].

Table no. 1:- Comparison of patient characteristics in the two groups.

| Patient characteristics | Group F (N=40) | Group N (N=40) | P value |
|-------------------------|----------------|----------------|--------------|
| Age (in years) | 41.2 ± 12.93 | 40.08 ± 11.06 | 0.6770 (N.S) |
| Sex (Male/Female) | 31/9 | 33/7 | 0.576 (N.S) |
| ASA grade (I/II) | 30/10 | 32/8 | 0.592 (N.S) |
| MPG (II/III/IV) | 27/7/6 | 34/4/2 | 0.163 (N.S) |

Data are n or mean \pm SD. MPG- Mallampati grade; ASA- American Society of Anesthesiologists; N.S-Non significant; S- significant

Table no. 2:- Data related to the AFOI procedure in the two groups.

| Parameters | Group F (N=40) | Group N (N=40) | P value |
|---------------------------|-----------------|-----------------|-------------------------|
| Mean comfort score | 1.65 \pm 0.7 | 2.2 \pm 0.79 | 0.0010 (S) |
| Intubation time (in min.) | 2.27 \pm 0.40 | 3.30 \pm 0.41 | < 0.001 (H.S) |
| Intubation attempt (1/2) | 36/4 | 35/5 | 0.723 (N.S) |

Table no 3:- Intubation scores in the two groups.

| Parameters | Group F (N=40) | Group N (N=40) | P value |
|-----------------------------|-----------------|-----------------|-------------|
| Vocal cord movements | | | |
| (1/2/3/4) ^a | (14/23/3/0) | (10/20/10/0) | 0.098(NS) |
| Mean \pm SD | 1.73 \pm 0.6 | 1.97 \pm 0.71 | 0.0940 (NS) |
| Coughing | | | |
| (1/2/3/4) ^b | (8/22/10/0) | (6/20/14/0) | 0.592 (NS) |
| Mean \pm SD | 2.05 \pm 0.68 | 2.2 \pm 0.69 | 0.3280 (NS) |
| Limb movements | | | |
| (1/2/3/4) ^c | (21/15/4/0) | (15/20/5/0) | 0.401 (NS) |
| Mean \pm SD | 1.58 \pm 0.68 | 1.75 \pm 0.67 | 0.2480 (NS) |

^a1=Open, 2=Moving, 3=Closing, 4=Closed, ^b1=None, 2=Slight, 3=Moderate, 4=Severe, ^c1=None, 2=Slight, 3=Moderate, 4=Severe. SD=Standard deviation

Table:4:- Observer's Assessment of Sedation(OAS) SCORE in both groups.

| OAS score | Group F (N=40) | Group N (N=40) | P value |
|--|----------------|----------------|--------------|
| 1 (Response after painful stimuli) | 0 (0%) | 0 (0%) | 0.022 |
| 2 (Response after mild shaking) | 8 (20%) | 3 (7.5%) | |
| 3 (Response only when name is spoken loudly) | 28 (70%) | 22 (55%) | |
| 4 (Lethargic response) | 3 (7.5%) | 13 (32.5) | |
| 5 (Appropriate verbal response to patient's name) | 1 (2.5) | 2 (5%) | |

Figure 1:- Mean HR in both groups during and after intubation.

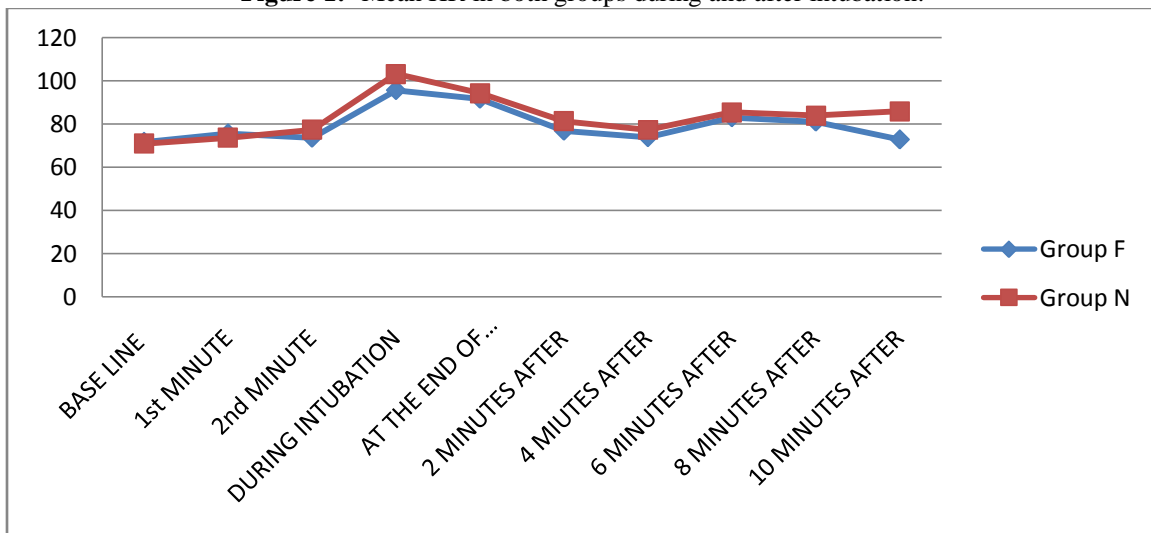


Figure 2:- Mean MAP in both groups during and after intubation.

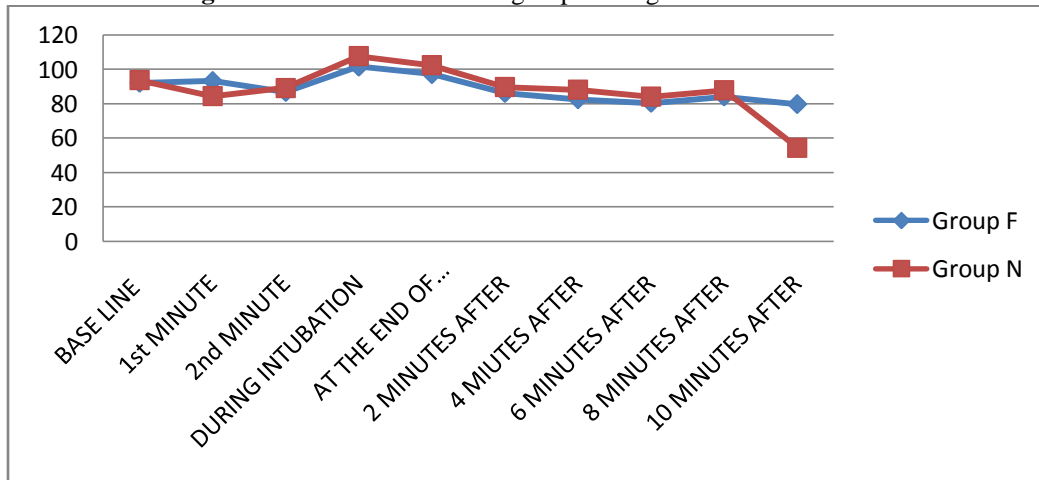


Figure 3:- Mean SPO2 in both groups during and after intubation.

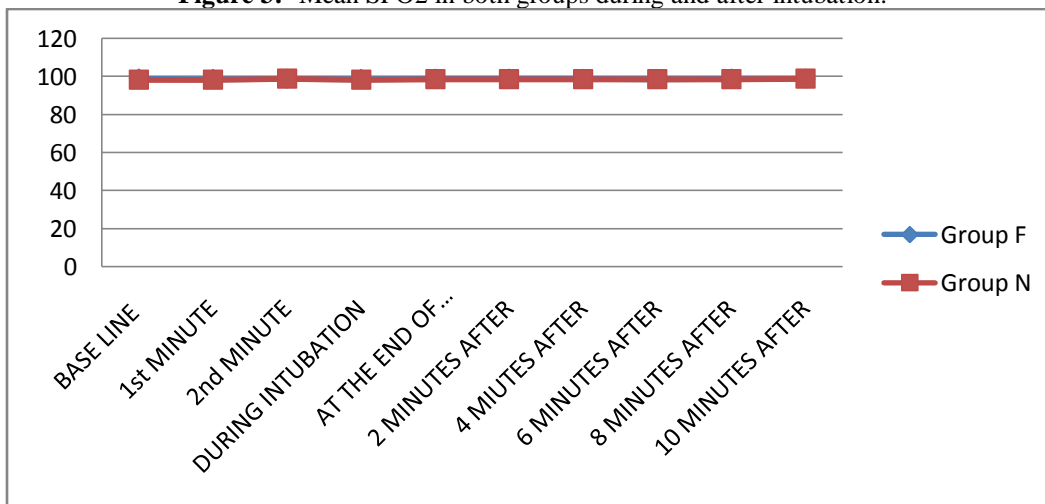


Figure 4:- Distribution of patient satisfaction score in both groups.



Discussion:-

Awake tracheal intubation with the aid of a fiberoptic device was first described by Murphy in 1967,^[5] who used a choledochoscope to facilitate nasotracheal intubation in patients with difficult airway.^{xiii} Since then, numerous subsequent authors have described the anesthetic techniques and experiences with awake FOB guided intubation. It offers several advantages over use of FOB after induction of general anesthesia in patients with cervical spine instability: Patient remains in a neutral position, minimizing the risk of neurological deterioration, patient's neurological status can be assessed after intubation, and spontaneous ventilation is preserved.^{xiv}

Conscious sedation is a major contributory factor for setting a scene for quiet, co-operative, communicative, pain free and spontaneously breathing patient undergoing AFOI. Fentanyl is a short acting opioid with immediate analgesia within 30-60 mins after single IV dose. Nalbuphine is a semi-synthetic opioid agonist-antagonist analgesic, which doesn't increase SBP, Pulmonary artery pressure, heart rate.

This prospective, randomized comparison study was aimed to evaluate the analgesic and sedative effects of fentanyl and midazolam to nalbuphine and midazolam in patients undergoing awake fiberoptic intubation. The studied population was divided into two groups: Group 1 and Group 2 based on the drug administered in Awake fiberoptic. In aggregate 80 patients were studied with 40 in each group. In our study undertaken, we have defined groups as F and N; wherein Group F was referred as Fentanyl (2 µg/kg) with midazolam (F) and Nalbuphine (0.2 mg/kg) with midazolam (N). Harpreet K et al.¹¹, Dhasmana S et al.^{xv}, Khanday SB et al.^{xvi} and Kaur S et al.¹ in their studies, they adopted similar methodology. In our study fentanyl and nalbuphine were given five minutes before commencing fiberoptic intubation. This time was considered optimum to administer these drugs to provide adequate sedation and analgesia and to prevent circulatory responses to tracheal intubation.^{15,xvii} In a study fentanyl (2 µg/kg) was given at different times before intubation and observed that optimal injection time five minutes before intubation.¹¹ Also, another trial done by Chawda PM et al. who stated that nalbuphine given in dose of 0.2 mg/kg 3-5 mins before laryngoscopy prevents stress response.^{xviii}

The mean comfort score and intubation time were significant lesser in Group F than Group N ($p < 0.05$). Our study shows that fentanyl and midazolam provided better intubating conditions as compared to nalbuphine and midazolam. Similarly, Kaur S et al.¹ observed fentanyl provided better intubating conditions as compared to nalbuphine and total Comfort Score when calculated showed a significant difference between the two groups during FOS and ET. Dhasmana et al.¹⁴ also observed in their study awake blind nasotracheal intubation in temporomandibular joint ankylosis patients under conscious sedation using fentanyl and midazolam that these drugs provide better intubating conditions in awake nasotracheal intubation.

Mean heart rate (per minute) between the two study groups showed significant differences at all the time intervals ($p < 0.05$) except at baseline. The maximum increase in heart rate at the end of intubation was 10.89% in group F & 16.62% in Group N in our study. Similarly, Harpreet kaur et al.¹¹ in their study the maximum increase in mean heart rate at the end of intubation was 10.89% in group F and 16.62% in group N. Also by Sharma N and Parikh H were seen maximum increase in the heart rate after intubation was 12.5% in group Fentanyl and 13.1% in group Nalbuphine.¹⁶ Thus heart rate in group Nalbuphine showed much higher positive variation than Fentanyl group. Ahsan-ul-Haq et al.^{xix} and Kay et al.^{xx} in their study compared the effects of fentanyl and nalbuphine and found significant rise in HR in patients of nalbuphine group, as compared to patients of fentanyl group.

MAP is a derived value and is important in relation to the autoregulatory responses of the heart, brain, and kidneys. In the present study, there was a significant difference at all intervals in MAP except baseline in patients of both fentanyl and nalbuphine groups. Our study showed better MAP control in group F. In accordance with our study, Channaiah et al.^{xxi} noted that intergroup MAP yielded significant attenuation in the fentanyl group for all recorded time periods. Chawda et al.¹⁷ observed significant increase in MAP after intubation in placebo compared to nalbuphine. Similarly, Ahsan-ul-Haq et al.¹⁸ noticed increase in MAP just after induction in placebo group which was significant whereas nalbuphine prevented this rise, in contrast to our study where nalbuphine could not attenuate the rise in MAP completely.

In the present study, mean SpO₂ level shows a nonsignificant variation at all study stages. However, the level remained within the normal limits at all times, and respiratory depression was not seen in any of the patients. These results were in line with the previous studies.^{11,15} In Group N, the initial fall in all the hemodynamic parameters is because of its strong and predominant kappa agonistic action. Rise in hemodynamic parameters after intubation is

due to sympathoadrenal stimulation.^{xxii} Fentanyl is a pure μ -agonist and is known to cause a decrease in arterial blood pressure, HR, systemic vascular resistance, and blood catecholamine levels while depressing the myocardial contractility and decreasing the cardiac workload, which may be the cause of the steady fall in all the hemodynamic parameters in the fentanyl group after 1 min of intubation.

In the study by Harpreet K et al.¹¹ reported fentanyl group had lesser intubation time and more comfortable during the procedure due to better sedation, analgesia, intubation score and hemodynamic profile. Hence, it provides better tolerance to the procedure. This was in concordance to observations by various other authors.^{xxiii,xxiv}

The scores of ease of AFOI, coughing severity and limb movement were comparable in both groups ($P > 0.05$). In the study done by Harpreet K et al.¹¹ observed comparable data in all three parameters. Bano N et al. reported the vocal cords movement is comparable in the groups, maximum number of patients with open vocal cords with least incidence of coughing and limb movement.²

Post-surgery, the satisfaction scores were evaluated and found group F patients had better satisfaction scores than group N but p value was insignificant. Similarly, Harpreet K et al observed comparable data in both groups. Both the groups had comparable satisfaction scores ($P=0.377$).¹¹ These were also similar to the scores obtained in study using similar technique for awake fiberoptic intubation.²²

Limitation:-

The study was not blinded which may have added to observational bias. The levels of catecholamines were not measured which would have shown more accurate attenuation, and the study was carried out on ASA classes I and II with no compromised state and hence, the population at potential risk was not included.

Conclusion:-

Fiberoptic intubation remains the accepted standard in elective airway management of the awake spontaneously breathing patient with an anticipated difficult airway. The two regimens used in this study provided comparable intubating conditions, better sedation and analgesia in group fentanyl for airway procedure events. Our study has shown fentanyl as the drug of choice for blunting of pressor response in such patients. Further studies with a larger sample size and which will overcome our limitations may be required to generalize the results and strengthen the literature.

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