



ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2019; 5(3): 337-342
www.allresearchjournal.com
Received: 20-01-2019
Accepted: 22-02-2019

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A prospective randomized study comparing Dexmedetomidine V/S. Combination of midazolam- fentanyl for ENT surgery under monitored Anaesthesia care

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Abstract

Analgesia and sedation are usually required for the comfort of all patients and surgeons during any surgery, particularly ENT surgery done under local anesthesia.

We conducted a prospective randomized study on 60 adult ASA grade I/II patients of either sex posted for various elective ENT surgeries under LA and monitored anesthesia care. They were randomly divided in to two equal groups as follows.

Group D: received IV dexmedetomidine infusion of 1mcg/kg over 10 min followed by 0.2mcg/kg/h during surgery.

Group MF: received IV midazolam 0.06mg/kg and IV fentanyl 1mcg/kg over 10 min followed by normal saline infusion at 2 ml/kg/h.

Sedation was maintained to keep Ramsay Sedation Score (RSS) to 3. Surgery was performed under LA. Intra operatively, if required, patients were given rescue analgesic fentanyl 1mcg/kg and rescue sedative midazolam 0.01mg/kg. Patients' vital parameters (PR, BP, SPO₂, ECG), VAS and sedation scores were recorded every 10 min. postoperatively all patients were interviewed to assess their satisfaction score about the technique. Surgeons were also asked for their opinion to assess their satisfaction about sedation technique.

We found that:

- Surgeons' and patients' satisfaction score were better in Group D than Group MF (9 and 7.5, and 9 and 8 respectively).
- Intraoperative pulse rate and BP were lower in Group D than in Group MF.
- In group D 8 patients required rescue LA infiltration. In group MF 12 patients required rescue LA infiltration.
- Number of patients requiring rescue analgesic and rescue sedative medication was higher in MF group than in group D (8 and 4, and 4 and 1 patient respectively).

None of the patients in both the groups had any complications requiring active treatment.

Keywords: Randomized, dexmedetomidine, analgesic

Introduction

Majority of ENT surgeries in adults are done under local anesthesia (LA) ^[1] supplemented with intravenous (IV) analgesia and sedation and monitored anesthesia care (MAC) ^[2]. Some of the patients may require general anesthesia (GA) ^[2] or in some cases LA technique may have to be converted in to GA if patient is uncooperative on the operation table. If surgery is done only under LA without any sedation and analgesic supplement patient may feel discomfort due to surgical pain, noise of suction, manipulation of surgical instruments, and application of traction and head-neck position necessary for adequate exposure of surgical site ^[3]. Commonly used drugs for IV sedation and analgesia during surgery like Opioids, Benzodiazepines, IV anesthetic drugs and Non-opioids in analgesic doses.

Use of these drugs is associated with side effects, for example, midazolam has quick onset of action but if it is administered repeatedly can cause prolonged sedation due to its relatively long half-life. If it is combined with opioids there is a risk of respiratory depression and even apnea leading to hypoxemia ^[4]. Propofol can cause cardio-respiratory depression especially if it is combined with opioids and midazolam ^[4].

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Over sedation during MAC can cause harm to the patient in many ways.

Dexmedetomidine hydrochloride has analgesic, sympatholytic and sedative property without any respiratory depression which is common in combination of opioids and midazolam [4]. Dexmedetomidine also reduces opioid requirement and stress response to surgery ensuring hemodynamic stability [5]. We therefore decided to undertake this study to compare efficacy of dexmedetomidine for IV sedation during MAC with that of commonly used combination of midazolam – fentanyl for IV sedation during MAC for ENT surgery.

Materials and Methods

The study was conducted on 60 adult patients posted for elective Ear, Nose and Throat (ENT) surgery belonging to either sex and in the age group of 20 to 60 years. Only those patients belonging to American Society of Anesthesiologists (ASA) grade I/II were accepted for this study. Prior approval of medical ethics committee of the institute was obtained. All patients were subjected to thorough pre anesthetic evaluation including relevant essential investigations. They were then explained about use of Visual Analogue Score (VAS) for purpose of recording their pain score. Informed consent was obtained from all the patients as per the format given in Appendices - A.

Inclusion criteria

- Patients between 20 to 60 years age.
- Both males and females.
- Patients of ASA physical status I and II.
- Patients posted for elective ENT surgery.

Exclusion criteria

- Patient's unwillingness to participate in the study.
- Patients with known sensitivity to local anesthetics and sedative/analgesic drugs to be used for study.
- Patients who are unable to understand use of VAS.
- Pregnant females and lactating mothers.
- Patients suffering from renal and hepatic disease.
- Patients who are on opioids, benzodiazepines and alpha 2 receptor agonists.
- Patients having bradycardia, intra cardiac conduction defects and low ventricular ejection fraction (EF <30%).
- Patients who are hypotensive and hypovolemic due to any cause.

Method of randomization

Patients were divided in to two equal groups according to the table of random numbers.

Group D: In these patients dexmedetomidine was used by intravenous (IV) infusion for intraoperative sedation.

Group MF: In these patients IV midazolam was used along with fentanyl to provide intraoperative sedation.

Materials required

- ❖ Anesthesia machine with Bain's breathing system.
- ❖ Source of oxygen.
- ❖ All resuscitation equipment – laryngoscope with different sizes of blades, endotracheal tubes of different sizes, stylets, local anesthetic jelly, Ambu bag, ventilator, oro pharyngeal airways, Laryngeal mask airways (LMAs).

- ❖ IV fluids –Ringer lactate (RL), dextrose normal saline (DNS), normal saline (NS), colloids.
- ❖ IV cannulae 20 and 18 G size.
- ❖ IV infusion sets.

Drugs

- Drugs for pre-anesthetic medication-glycopyrrolate, ondansetron, metoclopramide, ranitidine.
- Drugs for sedation – midazolam 10 ml vial (1 mg/ml), fentanyl 2 ml ampoule (50 mc/ml), dexmedetomidine ampoule 1 ml [100 mcg/ml].
- Syringes 2ml/5 ml/10 ml.
- Syringe infusion pump.
- Drugs for resuscitation –adrenaline, noradrenaline, atropine, mephentine, dopamine, dobutamine

Procedure

On the operation table patient's pulse rate (PR), Mean Arterial Pressure (MAP), peripheral arterial oxygen saturation (SPO₂), respiratory rate (RR) and electro cardiogram (ECG) were recorded.

Venous cannulation was done using 20 G venous cannula and slow IV infusion of ringer lactate (RL) was started at the rate of 2 ml/kg body weight.

In group D patients a loading dose of dexmedetomidine IV infusion was given at the rate of 1 mcg/kg over 10 min followed by maintenance infusion at the rate of 0.2 mcg/kg/hr. throughout surgery.

In group MF for intraoperative sedation IV midazolam was given in a dose of 0.06 mg/kg with fentanyl 1 microgram(mcg)/kg diluted in 10 ml NS over 10 min. followed by continuous IV infusion of NS at the rate of 0.2 ml/kg/hr throughout surgery.

During this 10 min period the patients were closely observed and assessed every 2 min for sedation using Ramsay Sedation Score (RSS) as follows.

Score Assessment

- 1 Patient agitated
- 2 Patient cooperative and tranquil
- 3 Patient sleeping but responds to verbal command
- 4 Brisk response to gabellar tap or loud voice
- 5 Sluggish response to gabellar tap or loud voice
- 6 No response

RSS 3 was taken as the target end point. In patients in whom the target end point was achieved before completing the loading dose the infusion was stopped and the dose of sedative drug administered was noted. Immediately after the loading dose was completed maintenance infusion was started in patients of both the groups and surgeon was requested to administer local anesthesia with 2% lignocaine-adrenaline (1:200000) 6-7 ml and proceed with surgery.

During surgery patient's clinical parameters such as PR, MAP were recorded initially every 2 min during loading dose infusion and then every 10 min and ECG, SPO₂ monitored continuously. In addition RSS was monitored every 10 min. In case RSS was noted to be <3, then midazolam 0.01mg/kg was administered IV as a rescue sedative in both the groups.

Intra operatively pain intensity was also assessed every 10 min using VAS as follows.

- 0 no pain
- 1-3 mild pain
- 4- 6 moderate pain

>7 severe pain

10 worst imaginable pain

If pain was more than 6-7 on VAS then surgeon was asked to give local infiltration of the same local anesthetic at surgical site. If patient is still complaining of pain rescue analgesia was given in form of fentanyl 1 mc/kg.

During surgery all the patients were observed for following adverse events-

- Bradycardia (PR<50 /min)
- Hypotension (SBP fall > 20% below base line)
- Hypertension (SBP increase > 20% above base line)
- Respiratory depression (RR < 8 breaths/min)
- Peripheral O₂ desaturation (SPO₂<90%)
- Any other adverse event.

In case of such adverse events following treatment was given immediately. For bradycardia atropine 0.3 mg IV and repeated if required. For hypotension rate of RL infusion was increased and IV ephedrine 3-5 mg was given. For respiratory depression oxygen flow was increased to 6 lit/min and bag- mask ventilation was used.

Approximately 15 to 20 minutes prior to end of surgery maintenance infusion of the study drug was stopped and patient was allowed to recover.

The patients were then shifted to post operation room for further observations and management.

After surgery surgeon was asked to grade surgical condition and satisfaction with this sedation technique on numerical rating scale (NRS) in which 0 on this scale meant least satisfaction and score of 10 meant maximum satisfaction.

Patients were also asked to grade their level of satisfaction on first postoperative day. This was the primary end point of our study.

Statistical analysis

For statistical analysis SPSS version 16.0 was used

Power analysis was based on the results of previous study.

Sample size was calculated based on population standard deviation of 1.1 80% power and 5% alpha error.

Hemodynamic and respiratory data was evaluated using unpaired t test for inter group and paired t test for within group comparison. P value < 0.05 was considered significant.

Review of literature

Monitored anesthesia care (MAC) is a specific anesthesia service for diagnostic or therapeutic procedures performed under local anesthesia along with sedation and analgesia titrated to a level that preserves spontaneous breathing and airway reflexes [American Society of Anesthesiologists (ASA) update 2008] ^[6]. MAC comprises of three basic components

- A safe conscious sedation
- Measures to allay patient's anxiety.
- Effective pain control

Midazolam ^[7]

A water soluble benzodiazepine with an imidazole ring in its structure. Imidazole ring gives stability in aqueous solution and rapid metabolism. IV doses should be sufficiently spaced to permit the peak effect to occur before repeating the dose. Midazolam is extensively bound to plasma proteins (96-98%). The short duration of midazolam after a single dose is due to its high lipid solubility leading to rapid

redistribution from brain to other inactive tissue sites and also due to rapid clearance from liver. Elimination half time is 1-4 hours which is much shorter, Elimination $\frac{1}{2}$ time, volume of distribution and clearance of midazolam are not altered by renal failure.

Most commonly used benzodiazepine in pre anesthetic medication IV. For conscious sedation for surgery under local/regional anesthesia. Dose is 1.0 to 2.5 mg. Onset is within 30-60 sec, peak effect is at 3-5 min and duration of sedation is 15 to 80 min. The most common side effect seen is ventilatory depression due to decrease in hypoxic drive which is more exaggerated in COPD patients. Advancing age increases the sensitivity to hypnotic effect of midazolam.

Fentanyl ^[8]

Fentanyl is a phenyl piperidine derivative, synthetic opioid agonist that is structurally related to meperidine. Fentanyl is highly lipid soluble and has a low molecular weight. It binds to the specific opioid receptors located throughout central nervous system and other tissues and produce effective analgesia, with little sedation.

It can be administered via intravenous, transmural, transdermal, epidural and intrathecal. A single dose of fentanyl administered intravenous has a more rapid onset and shorter duration of action than morphine Short duration of action of single dose of fentanyl reflects its rapid redistribution to inactive tissues such as fat and skeletal muscles. Elimination $\frac{1}{2}$ time - 3.1-6.6hrs. 1-2 μ g/kg IV to provide analgesia.

Dexmedetomidine ^[9]

Dexmedetomidine is a highly selective alpha-2 agonist that provides anxiolysis and cooperative sedation without respiratory depression. It decreases central nervous system (CNS) sympathetic outflow in a dose-dependent manner and has analgesic effects best described as opioid-sparing. There is increasing evidence that dexmedetomidine has organ protective effects against ischemic and hypoxic injury, including cardio protection, neuro-protection, and reno-protection. Alpha 2-adrenoceptors are found in many sites through CNS, density being more in Locus Ceruleus, the predominant noradrenergic nuclei of the brainstem and an important modulator of vigilance and nociceptive neurotransmission. Presynaptic activation of the alpha2-Adrenoceptor in the Locus Ceruleus inhibits the release of norepinephrine (NE) and results in the sedative and hypnotic effects and terminates the propagation of pain signals leading to analgesia. Postsynaptic activation of alpha2-adrenoceptors in the CNS results in decrease in sympathetic activity leading to hypotension and bradycardia and also augmentation of cardiac-vagal activity. Combined these effects can produce analgesia, sedation and anxiolysis. Elimination half-life of approximately 2 hours with short α -half-life of 6minutes.

Its role and mechanism as a sedative, hypnotic, amnestic, analgesic and sympatholytic has been explained. The responses of activation of α -adrenoceptors in other areas leads to decreased salivation, secretion, intraocular pressure, platelet aggregation, shivering threshold, bowel motility and increased glomerular filtration.

It is sole agent for procedural sedation: Due to its faster action, faster recovery and discharge times, dexmedetomidine has emerged as a sole agent for

procedural sedation. It has been approved for use as a sedative-analgesic and/or total anaesthetic in adults and Pediatric patients undergoing small minimally invasive procedures, with or without the need for tracheal intubation. It is a safe sedative alternative to benzodiazepine/ opioid combinations in patients undergoing monitored anaesthesia care for a multitude of procedures, because of its analgesic properties, “co-operative sedation”, and lack of respiratory depression.

Parikh and colleagues studied the effect of DEX against the traditional midazolam-fentanyl combination for providing adequate sedation and analgesia in tympanoplasty operation under MAC. They found a higher patient and surgeon satisfaction with DEX indicating a qualitatively better sedation profile but there were significant falls in heart rate and blood pressure warranting close monitoring. DEX did not show significant advantage over midazolam-fentanyl in terms of respiratory depression but there was no incidence of bradypnea in either of the groups [10].

A multicentric trial on 321 patients undergoing a broad range of surgical or diagnostic procedures under MAC revealed that dexmedetomidine provides greater patient satisfaction, less opioid requirements and respiratory depression than placebo rescue with midazolam and fentanyl [11]. DEX was well tolerated over different age groups and hypotension and bradycardia caused by its infusion was easily manageable.

Recently Gupta K and colleagues [12] evaluated the clinical effects of dexmedetomidine IV infusion during middle ear surgery using operating microscope under general anesthesia in 32 adult patients. They used a dose of 0.5mcg/kg/h after induction of GA till 20 min before completion of surgery. They concluded that DEX infusion was safe to provide oligoemic surgical field for better visualization under operating microscope for middle ear

surgery keeping the hemodynamic variations within physiological range. It also reduced the requirement of isoflurane and recovery from anesthesia was complete and smooth.

Results

Both the groups (Group D and Group MF) were comparable with respect to their age, sex and body weight with no statistically significant difference between the two (P>0.05).Types of ENT surgeries performed in both the groups are Tympanoplasty, Mastoidectomy, Septoplasty and FESS.

Mean duration of surgery and base line vital parameters (PR, MAP, and SPO2) in both the groups on the operation table were comparable between the two groups.

In group D loading dose of DEX was given over 10 min and during this period sedation score (RSS) was recorded every 2 min. Out of 30 patients in this group 5 patients were cooperative and tranquil (RSS=2) and 25 patients were comfortably sleeping, responding to verbal command (RSS=3).In patients having RSS=2, midazolam 0.01mg/kg was administered IV. In group MF also RSS was recorded every 2 min during first 10 min. In this group 8 patients had RSS =2 requiring additional dose of midazolam 0.01mg/kg. Twenty two patients had RSS=3.

During surgery in both the groups PR, MAP were recorded every 10 min till the end of surgery is shown in Tables 1 and 2 and in Figures 1 and 2. In all these patients SPO₂ was monitored continuously from commencement of loading dose of the study drug till the end of surgery. In group D, there was no fall in SPO₂ below 97% any time during surgery. In group MF, however, there were transient episodes of fall in SPO₂ to 92% in most of the patients which could be improved by increasing oxygen flow to 6 lit/min and asking the patient to take deep breaths.

Table 1: Comparison of pulse rate at various time interval in study group.

Time (mins)	Group D		Group MF	
	Mean	SD	Mean	SD
0	79.26	1.80	82.3	2.76
5	76.76	1.82	80.03	2.42
10	68.46	2.46	80.7	2.39
20	73	2.12	81.46	3.91
40	76.3	2.20	80.46	2.71
60	77.06	2.56	81.63	3.41
80	80.93	1.94	83.3	2.91

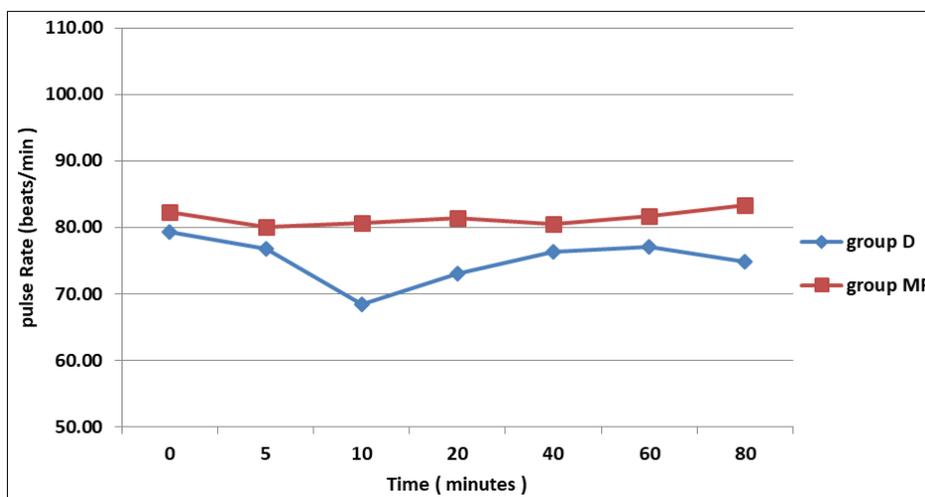


Fig 1: Line diagram showing comparison of mean of pulse rate at different time intervals (Group D and Group MF).

Table 2: Comparison of MAP at various time interval in groups.

Time (Mins)	Group D		Group MF	
	Mean	SD	Mean	SD
0	98.16	3.01	97.5	1.43
5	96.16	2.63	94.96	1.18
10	79.5	3.10	80.03	2.15
20	78.46	3.05	81.8	2.72
40	77.1	2.13	83.63	2.74
60	77.9	1.89	86.33	2.41
80	80.93	1.68	89.1	3.32

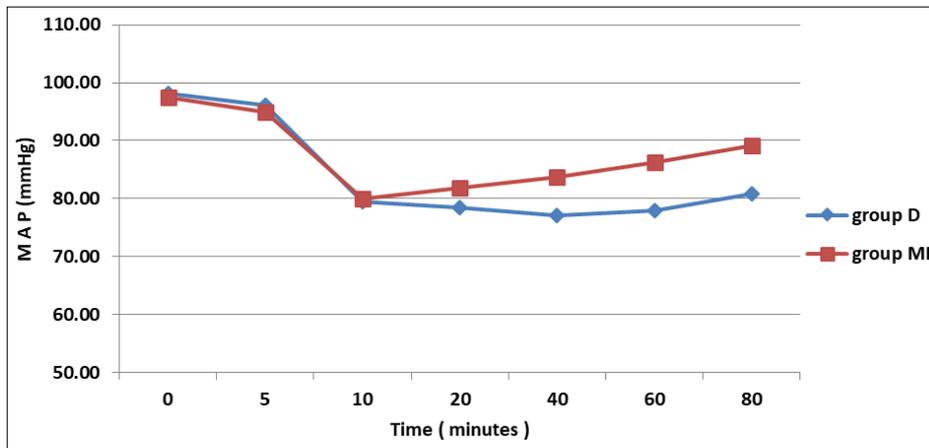


Fig 2: Line diagram showing comparison of MAP at different time intervals in groups.

Mean VAS recorded in both the groups at 10 min interval intra operatively is shown in Table 3.

Table 3: Comparison of mean of VAS score at different time intervals in groups.

Parameter	Group D		Group MF		
	Mean	SD	Mean	SD	P value
0	0	0	0	0	0
5	1.34	0.80	1.58	0.89	0.277
10	1.34	0.80	1.93	1.12	0.022
20	1.41	1.00	2.51	1.73	0.004
40	1.62	1.35	2.59	1.77	0.02
60	1.68	1.24	2.41	1.56	0.049
80	1.89	1.35	2.75	1.91	0.049

Eight patients in group D and 12 patients in group MF required local anesthetic (LA) infiltration by the surgeon. Out of these patients only 4 patients in group D needed rescue fentanyl (one top-up dose in 3 patients and top-up doses in 1 patient) and one of these patients required one rescue dose of midazolam as RSS in this patient was 2. In group MF, out of 12 patients who required rescue LA 8 patients had to be given rescue fentanyl injection (one top-up dose in 5 patients, 2 top-ups in 2 patients and 3 top-ups in one patient). Out of these 8 patients 4 patients were given one dose of midazolam to achieve RSS of 3 Thus more number of patients in midazolam-fentanyl group required rescue LA infiltration as well as rescue doses of fentanyl and midazolam. Table 4

Table 4: Rescue sedatives & analgesics. Data expressed as number (Proportion)

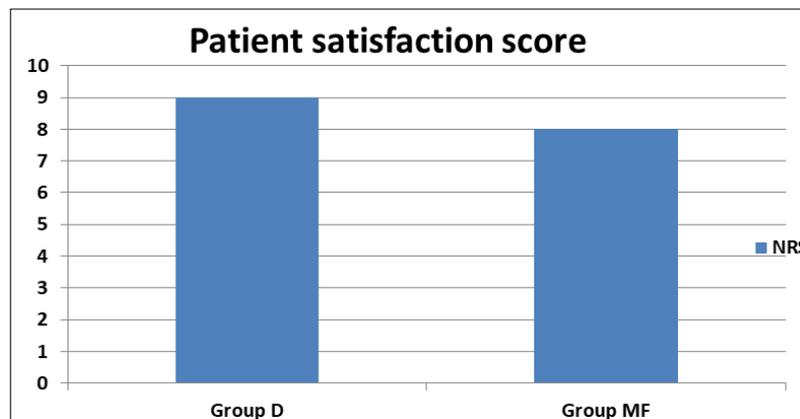
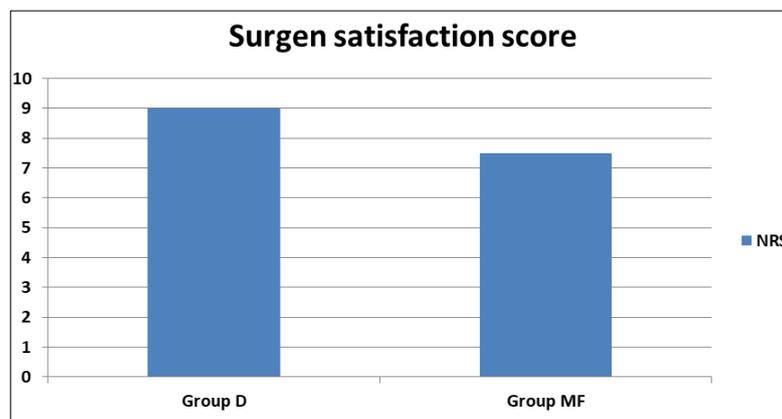
	Group D	Group MF	P value
Rescue Midazolam			
Yes / no	1 / 29	4 / 26	0.22
No. of top-ups (1/2/3)	1 / 0 / 0	4 / 0 / 0	
Rescue LA infiltration			
Yes / no	8 / 22	12 / 18	0.03
Rescue fentanyl			
Yes / no	4 / 26	8 / 22	0.11
No. of top-up (1/2/3)	3 / 0 / 1	5 / 2 / 1	

There were no major complications or side effects due to drugs used for sedation. In recovery room all the patients were observed and closely monitored with pulse Oximeter and non-invasive BP monitor for one hour. They were then shifted to postoperative ward after an hour and stable. On the next day, all the patients were interviewed for their overall experience about sedation for surgery and they were

asked to rate their satisfaction score using Numerical Rating Score (NRS). The operating surgeons were also asked about their experience and level of comfort during surgery. NRS expressed by patients and surgeons is given in Table no 5 and Figures 3 and 4. Patients' as well as surgeon's level of satisfaction was significantly higher in dexmedetomidine group as compared to midazolam-fentanyl group.

Table 5: patient & surgeon satisfaction score & time to post- operative rescue analgesics.

Group D (n = 30) Median (IQR)		GROUP MF (N = 30) Median (IQR)	P Value
Patient satisfaction score : NRS (1 – 10)	9 (8 – 10)	8 (6 – 9)	.0001
Surgeon satisfaction score : NRS (1 – 10)	9 (8 – 10)	7.5 (6 – 9)	.0001
Group D (n = 30) Mean (SD)		Group MF (n = 30) Mean (SD)	P Value

**Fig 3:** Bar diagram showing patients satisfaction score (NRS) in groups.**Fig 4:** Bar diagram showing surgeon satisfaction score in groups.

Conclusions

From the present study we can conclude that:

- ❖ Dexmedetomidine when used by continuous IV infusion for sedation-analgesia during ENT surgery for MAC is safe and better than midazolam-fentanyl combination.
- ❖ Patient and surgeon satisfaction is better with DEX than with midazolam-fentanyl combination.

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