

## Nalbuphine and pentazocine in opioid benzodiazepine sedative technique in ear surgery under local anaesthesia –a double blind comparison

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### Abstract

**Introduction:** The use of local anaesthesia and intravenous sedation for middle ear surgeries is long established and has many advantages. Good sedation is mandatory to alleviate different discomforts associated with these surgeries under local anaesthesia. Opioid- benzodiazepine sedation is common technique used for many procedures. Both pentazocine and nalbuphine are nalorphine like opioid agonist antagonist drugs. This study was undertaken with an aim to compare two opioid-benzodiazepine sedative techniques, 'pentazocine-diazepam' and 'nalbuphine-diazepam' for middle ear surgery under local anaesthesia.

**Materials and Method:** Sixty patients scheduled for elective middle ear surgery between 15 to 50 years age group, of either sex having American society of anaesthesiologists physical status of 1 or 2 were included in the study to receive either pentazocine-diazepam (Group A) or nalbuphine-diazepam (Group B) sedation along with local anaesthesia.

**Results:** Ramsay sedation score was satisfactory and comparable in both groups. Respiratory and spo2 changes were safe and comparable in both groups. Intra operative discomforts were minimal and easily manageable in both groups. Analgesic efficacy was good with nalbuphine having statistically significant longer duration of post operative analgesia than pentazocine (p less than 0.00001). Post operative side effects were minimal and comparable in both groups.

**Conclusion:** Both regimens gave satisfactory results in terms of sedation, analgesic efficacy, respiratory and spo2 changes with minimal discomforts and nalbuphine being superior in terms of post operative analgesic duration.

**Keywords:** Pentazocine, Nalbuphine, Sedation, Middle ear surgery.

### Introduction

Common middle ear surgeries include tympanoplasty, mastoid exploration, stapedectomy, grommet insertion etc. Most of the ear surgeries are done under local anaesthesia and has many advantages.<sup>(1)</sup> Patient may experience various discomforts like a sense of noise, anxiety, dizziness, backache, claustrophobia or earache.<sup>(2)</sup> To alleviate these problems good sedation is mandatory. Opioid-benzodiazepine combination being having sedative, amnesiac, anxiolytic and analgesic effect<sup>(3,4)</sup> is common technique used for multiple procedures. Pentazocine-diazepam combination is commonly used. Pentazocine, the N allyl derivative of narcotic analgesic phenazocine, is strong analgesic with weak narcotic antagonist activity. It is used for moderate to severe pain. It is agonist on kappa receptor and weak antagonist on mu receptor. With increasing dose it has ceiling effect on respiratory depressant action. It is 1/6<sup>th</sup> to 1/3<sup>rd</sup> as potent as morphine. Pentazocine increases cardiac workload, blood pressure and pulmonary artery pressure.<sup>(4,5)</sup> Nalbuphine is a semi synthetic agonist-antagonist opioid analgesic of phenanthrene series. It is antagonist on mu receptor and agonist on kappa receptor. It is structurally similar to opioid antagonist naloxone, differing in having a cyclobutylmethyl group on nitrogen containing ring instead of the allyl group of naloxone. Its analgesic efficacy is comparable to morphine on milligram basis. It is used for moderate to severe pain. Being agonist-antagonist it has ceiling effect on respiratory depression with increasing dose

beyond particular dose.<sup>(4,6)</sup> Being pure mu antagonist it is preferred for opioid induced pruritus.<sup>(7)</sup> It has favorable cardiovascular profile. It is suitable alternative to fentanyl for sedation and analgesia in medically compromised patients.<sup>(8)</sup> With this background we have decided to study different combinations of opioid-benzodiazepine sedative techniques in ear surgery under local anaesthesia. Two trials in patients with postoperative pain suggested that nalbuphine is about three times as potent as pentazocine following intramuscular or intravenous injection.<sup>(6,9,10)</sup> But more recent work suggest a ratio of nearer 2:1. In the present study, the drugs were compared in a dose ratio of 2.5:1 that is pentazocine 0.5mg/kg and nalbuphine 0.2mg/kg along with diazepam 5mg intravenously.

### Aims and Objectives of the study

Aims and objectives of our trial were to study- A) efficacy of benzodiazepine-opioid intravenous sedation B) changes in respiratory rate and oxygen saturation C) intra operative discomforts if any D) postoperative analgesic duration E) side effects if any.

### Materials and Method

This prospective randomized double blind study was undertaken after institutional ethical committee approval dated 15/10/2015. Study was conducted on sixty patients of either sex presented for elective middle ear surgery (tympanoplasty/ mastoidectomy) after

written informed valid consent with following inclusion or exclusion criteria-

**Inclusion criteria:** 1) age group between 15 to 50 years  
2) weight of 40 to 70 kg 3) ASA status of 1 or 2.

**Exclusion criteria:** 1) Pediatric and geriatric debilitated patients 2) patient having known drug allergy 3) patient having history of respiratory problem.

After complete preoperative evaluation, investigations and written informed valid consent patients were randomly divided into two groups of 30 each as group A or group B by picking up random numbered chits labeled as either A or B. To maintain double blinding study, drug was prepared by anaesthetist who was not involved in the study after picking up chit by himself. Both patient and data collecting anaesthetist were blind about the group allocation. After taking patient on operation table multipara monitor (NIBP/PR/SPO2/RR/ECG) applied and baseline parameters noted. Intravenous line secured with 20 G intracath and infusion of ringer lactate started with injection ranitidine 50mg and injection ondansetron 4mg added to it. With randomization and blinding, either of the study drugs given along with diazepam 5mg intravenously. Group A patients received intravenous sedation with diazepam 5mg and pentazocine 0.5mg/kg whereas group B patients received intravenous sedation with diazepam 5mg and nalbuphine 0.2mg/kg. After 10 minutes local anaesthesia given with 1% lignocaine with 1:1,00,000 adrenaline with 26 Gauge needle. Intra operatively response to needle prick noted while giving local anaesthesia. Response as 'no' or 'tolerable pain' interpreted as adequate analgesia and response as 'behavioral changes', 'vocal response' or 'strong facial grimacing' interpreted as inadequate analgesia.

Also respiratory rate and oxygen saturation changes noted at 0 minute (baseline), 1, 2, 5, 10, 30, 60

minute post sedation and at the end of surgery. Fall in spo2 below 90% considered as clinically significant.

Intra operatively sedation scale noted as Ramsay 1 to 6 at 10, 30 and 60 minute post sedation.

Ramsay sedation scale: Ramsay 1- conscious, agitated, restless.

Ramsay 2- conscious, oriented, tranquil.

Ramsay 3- responds to verbal commands only.

Ramsay 4- asleep, brisk response to light glabellar tap.

Ramsay 5- asleep, sluggish response to light glabellar tap.

Ramsay 6- asleep, no response to glabellar tap.

Ramsay 1 to 3 being awake interpreted as poor sedation whereas Ramsay 4 to 6 being asleep interpreted as good sedation.

Intraoperative discomforts like intense ear noise, headache, neck pain, backache, positional discomfort, nasal and upper lip itching, claustrophobia, earache etc. as complained by patient also noted. Also postoperatively duration of first onset of pain noted as complained by patient. After onset of post operative pain rescue analgesic given with injection diclofenac sodium 75mg intramuscular.

Intra operative and post operative side effects if any were noted.

## Results

Data was collected and expressed as mean with standard deviation (SD).

**Statistical analysis:** Statistical analysis done using IBM SPSS version 20.0 software (AppOnFly, Inc Online IBM SPSS started in 2005). Unpaired t value and significant (2-tailed) value calculated.

In our study, 26 patients underwent tympanoplasty and 4 underwent mastoidectomy in both groups. Demographic parameters like age, sex and weight were comparable in both groups (Table 1).

**Table 1: Demographic parameters**

Parameter	Group A (Pentazocine) Mean±SD	Group B (Nalbuphine) Mean±SD	Test of significance value
Age (years)	30.13±10.96	30.63±7.69	0.4193
Weight (kg)	56.66±5.46	56±4.98	0.3117
Sex (M/F)	7/23	7/23	

Duration of surgery was comparable in both groups (Table 2).

**Table 2: Duration of surgery**

Parameter	Group A (Pentazocine) Mean±SD	Group B (Nalbuphine) Mean±SD	Test of significance value
Duration of surgery (min.)	103.83±35.68	103.5±35.74	0.4856

**Sedation:** In both groups Ramsay sedation scale was comparable at 10, 30 and 60 minute post sedation and statistically there was no significant difference (Table 3).

**Table 3: Ramsay sedation scale**

Ramsay sedation scale at	Group A (Pentazocine) Mean±SD	Group B (Nalbuphine) Mean±SD	Unpaired t value	Sig.(2-tailed)
10 minute	4.3±0.8	4.3±0.8	0.15	0.875
30 minute	4.8±0.7	4.9±0.8	0.49	0.312
60 minute	4.6±0.2	4.6±0.2	0.19	0.845

Two patients in each group had Ramsay sedation score of 3 at 10 minutes post sedation, but later on they became fall asleep. Also 3 patients in each group had Ramsay score of 3 throughout the procedure, but the patients were tranquil and responding to verbal commands only and all tolerated the procedure very well. This score of 1 to 3 was considered as poor sedation. Rest all patients had good sedation. Thus there was no significant difference between two groups in efficacy of IV sedation.

**Respiratory rate and oxygen saturation changes:** Respiratory rate and oxygen saturation changes were safe and comparable in both groups without any statistically significant difference (Table 4 & 5).

**Table 4: Respiratory rate changes**

Respiratory rate at	Group A (Pentazocine) Mean±SD	Group B (Nalbuphine) Mean±SD	Unpaired t value	Sig.(2-tailed)
0	16.7±1.2	17±1.1	0.77	0.442
1	16.3±1.3	16.4±1.3	0.19	0.846
2	15.3±1.29	15.4±1.49	0.27	0.391
5	14.4±1.5	14.9±1.8	1.13	0.249
10	15.5±1.5	16.16±1.05	1.79	0.078
30	16.5±1.3	16.8±0.99	0.98	0.327
60	16.7±1.2	16.8±1.1	1.1	0.149
At end	16.7±1.2	16.8±1.1	1.9	0.548

**Table 5: Spo2 changes**

Oxygen saturation changes at	Group A (Pentazocine) Mean±SD	Group B (Nalbuphine) Mean±SD	Unpaired t value	Sig.(2-tailed)
0 min.	99±1	99.4±0.3	1.2	0.202
1 min.	98±1.2	97.8±1	0.77	0.458
2 min.	97±0.8	96.6±0.8	1.1	0.249
5 min.	96.4±1	96.2±0.8	1.5	0.765
10 min.	97.4±0.5	97±0.4	0.19	0.712
30 min.	99±1	98.8±1	1.3	0.654
60 min.	99.06±1.2	99±0.3	0.70	0.080
At end	99.13±1.1	99.4±0.8	1.2	0.879

Total three patients in each group had fall in spo2 below 90% for transient period only. One patient in pentazocine group had fall in spo2 up to 88% and another up to 87%, whereas in nalbuphine group one patient had fall in spo2 up to 89% and another up to 86% between 5 and 10 minute post sedation. This fall in spo2 was transient only and got autocorrected by reactivation of respiratory drive. One patient in each group had fall in spo2 up to 80% at 5 minute which responded immediately by reactivation of respiratory drive and with oxygen supplementation by nasal prong for a minute only. These episodes were occurred in first 10 minutes only. No patient desaturated later on.

**Intraoperative discomfort:** One patient (3.33%) of tympanoplasty in each group had pain on annulus handling, but it was transient and relieved on application of 4% lignocaine soaked gel foam. One patient (3.33%) of MRM in each group complained of noise during drilling of mastoid bone, but on explanation of procedure they tolerated it well. One patient in each group (3.33%) complained of neck pain, which relieved on turning the head for some time to normal position i.e. eyes facing to ceiling. One patient in each group (3.33%) had backache with positional discomfort. All these patients were of mastoidectomy (MRM) surgery with prolonged duration. Five patients in pentazocine group (16.66%) had transient nasal or upper lip itching as against three patients (10%) in nalbuphine group and this was relived easily on rubbing of itch site by finger and was not troublesome.

**Analgesic efficacy:** In pentazocine group one patient had behavioral changes of withdrawing head and lifting limbs, one patient had strong vocal response and two had strong facial grimacing on needle prick and local infiltration (inadequate analgesia of needle prick-13.33%). In nalbuphine group one patient had strong vocal response and two had strong facial grimacing on needle prick and local infiltration (inadequate analgesia of needle prick-10%). Rest all patients had adequate analgesia to needle prick and local infiltration. Postoperatively mean duration of analgesia in nalbuphine group was longer than pentazocine group with statistically significant difference (p less than 0.00001).

**Table 6: Duration of first onset of pain**

	<b>Group A (Pentazocine) Mean±SD</b>	<b>Group B (Nalbuphine) Mean±SD</b>	<b>Unpaired t value</b>	<b>Sig.(2-tailed)</b>
First onset of pain (minute)	239±36.72	352±61.46	8.66	p less than 0.00001

**Side effects:** Postoperatively three patients in pentazocine group (10%) had single episode of vomiting. In nalbuphine group two patients had single episode of vomiting and one patient had nausea (Total-10%). All these responded to additional dose of ondansetron.

## Discussion

Middle ear surgeries are commonly done under local anaesthesia. The advantages of local anaesthesia are less bleeding, cost effectiveness, postoperative analgesia, early mobilization and ability to test facial integrity and hearing intraoperatively.<sup>(1)</sup> So as to maintain these advantages, various discomforts<sup>(2)</sup> associated with middle ear surgery under local anaesthesia needs to be alleviated by giving adequate sedation and analgesia. Also proper explanation of the procedure preoperatively is very important so as to have good patient co-operation. Benzodiazepine-opioid combination is having sedative, amnesiac, analgesic and anxiolytic<sup>(3,4)</sup> properties with smooth recovery. Pentazocine and nalbuphine are nalorphine like opioid agonist-antagonist drugs. Being opioid agonist-antagonist they have advantages of less psychomimetic effects, less itching, ceiling to respiratory depressant property etc. besides maintaining sedation and analgesia. In our study we have compared these both drugs used in combination with diazepam for sedation in middle ear surgeries done under local anaesthesia. In our study sedative efficacy of pentazocine-diazepam and nalbuphine-diazepam combination is comparable (Table 3). Our results were comparable to previous studies.<sup>(11,12)</sup> Opioid-benzodiazepine combinations is having respiratory depression effect. So as to avoid marked desaturation, controlled dose selection is important. In our study respiratory and oxygen saturation changes in both groups are comparable (Table 4, 5) and there was no episode of apnea requiring mask ventilation. Though three patients in each group had desaturation below 90%, it was transient and got autocorrected by stimulation of respiratory drive and transient oxygen supplementation if required. In rest all patients spo<sub>2</sub> remained above 90%. Still we recommend cautious use of opioid-

benzodiazepine combination in elderly patients and those having pulmonary compromise. Our results were comparable to previous studies.<sup>(11)</sup> Joan L Graham et al<sup>(11)</sup> compared benzodiazepine-opioid sedative combination for invasive radiological procedure and found comparable respiratory and spo<sub>2</sub> changes with nalbuphine and pentazocine. They also recommended cautious use of it in elderly and compromised patients with availability of supplementary oxygen.

Yung MW<sup>(2)</sup> made survey of patients and surgeons undergone middle ear surgery under local anaesthesia. He found intense sensation of noise during operation in 29.6% patients, anxiety in 24% patients, dizziness in 14.8% patients, backache in 13.9% patients, claustrophobia in 9.3% patients and earache in 1.9% patients. In our study efficacy of sedative, analgesic, anxiolytic and amnesiac properties of opioid-benzodiazepine combination was very good and thus incidents of intra operative discomforts were very less in both groups and were comparable. These intra operative discomforts were relieved by simple measures. Annulus pain can be avoided by using adequate volume of local infiltration; applying 4% lignocaine soaked gel foam and good sedation. Incidence of neck pain, backache and positional discomfort was mainly found on prolonged surgical duration. This can be avoided by good sedation and in between allowing for some change in position as long as it doesn't compromise the surgical field, if the surgery is prolonged. Noise sensation can be avoided with good sedation and proper explanation to patient that noise will not cause pain. Incidence of opioid itch varies from 2% to 100% and it varies with type of opioid, dose and route of administration. Injectable opioid have high incidence than chronic oral opioid. Both peripheral and central action is responsible for opioid itch. Peripheral release of histamine from mast cells and central mu receptor mediated action are said to be proposed causes of opioid itching.<sup>(13)</sup> Mu antagonist are specially used for relieving this itch. Studies have shown, pentazocine and nalbuphine to be used in relieving intrathecal morphine induced itch.<sup>(7,14)</sup> Pentazocine is weak mu receptor antagonist. Nalbuphine being pure mu antagonist found to be more

effective in relieving this itch.<sup>(15)</sup> In our study incidence of this opioid itch was less in nalbuphine group (10%) than pentazocine group (16.66%) and it was not troublesome.

90% patients in nalbuphine group had adequate analgesia of needle prick and local infiltration as against 86.67% patients in pentazocine group. Patients in nalbuphine group were comparatively more pain free (Table 6) for significantly longer duration than pentazocine group (352±61.46 min versus 239±36.72 min with significance value of less than 0.00001). Our results were comparable to previous studies.<sup>(10,12)</sup> Tammisto T et al<sup>(10)</sup> compared analgesic effects of intravenous nalbuphine and pentazocine for post operative pain found longer analgesic duration with nalbuphine. Hook PC ET al<sup>(12)</sup> compared intravenous nalbuphine and pentazocine with midazolam for oral surgery under local anaesthesia with sedation. They found statistically more significant pain free period post operatively in nalbuphine group.

Post operative nausea-vomiting incidence (10% in each group) was comparable in both groups and was not troublesome.

## Conclusion

Thus we conclude that nalbuphine is effective alternative to pentazocine when used in combination with diazepam and is superior to pentazocine in view of prolonged post operative analgesic duration.

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