ORIGINAL ARTICLE

Combination of Midazolam and Butorphanol for Sedation for Tympanoplasty under Monitored Anaesthesia Care

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Abstract:

Background: Tympanoplasty is routinely done under local anaesthesia with sedation due to various advantages. Systemic analgesics and sedatives are generally given to improve the patient comfort. *Aim & Objectives:* To determine the effectiveness of combination of midazolam and butorphanol for sedation and to assess the sedation technique using midazolam and butorphanol for tympanoplasty under monitored anaesthesia care. *Material and Methods:* One hundred patients scheduled for tympanoplasty under local anaesthesia were given bolus doses of intravenous midazolam 0.03 mg/kg and butorphanol 0.03 mg/kg followed by midazolam infusion at 0.01 mg/kg/hr. If required, additional bolus doses of 0.01 mg/kg of both midazolam and butorphanol were given to achieve desired sedation and analgesia. The total dosage of midazolam and butorphanol, vital parameters, sedation score using Ramsay sedation score, pain score and surgeon satisfaction score using Numeric rating scale were recorded. *Results:* Ninety nine patients underwent tympanoplasty satisfactorily with sedation technique. Only one patient needed conversion to general anaesthesia. The mean duration of surgery was 92.7±8.16 minutes. The total midazolam and butorphanol dosages were 2.45±0.233 mg and 1.65±0.179 mg respectively. The desired Ramsay Sedation Score (RSS) of 3 and pain score Numerical Rating Scale (NRS) = 2.82±0.72) were achieved within 4-8 minutes. No side effects of excessive sedation were observed. *Conclusion:* Combined use of midazolam and butorphanol in low doses produces adequate sedation for tympanoplasty under local anaesthesia without serious adverse effects.

Keywords: Tympanoplsty, Midazolam, Butorphanol, Monitored Anaesthesia Care

Introduction

According to American Society of Anaesthesiologists (ASA), Monitored Anaesthesia Care (MAC) is a planned procedure under local anaesthesia together with sedation and analgesia [1]. MAC may be applied for various ENT surgeries in which an adequate sedation and analgesia without respiratory depression are desirable for comfort of both the patient and the surgeon [2].

Tympanoplasty or reconstruction of perforated eardrum can be done under local anaesthesia with sedation under MAC or general anaesthesia in children or uncooperative patients [3, 4]. Many surgeons prefer using local anaesthesia for middle ear surgery owing to various advantages such as less surgical bleeding and feasibility to test hearing and facial nerve integrity during the surgery itself with minimum patient discomfort.

Patient discomfort is usually due to pain, noise due to drilling, claustrophobia or manipulation of head and neck position [5].

Anaesthetic drugs are administered during procedures under MAC with the goal of providing analgesia, sedation, and anxiolysis and ensuring rapid recovery without side effects. Systemic analgesics are often used to reduce the discomfort associated with the injection of local anaesthetics and prolonged immobilization. Sedative-hypnotic drugs are used to make procedures more tolerable for patients by reducing anxiety and providing a degree of intraoperative amnesia while allowing them to rest or sleep during the operation.

Commonly used medications for sedation and analgesia during middle ear surgery under monitored anaesthesia care include benzodiazepines, opioids, propofol, α-2 agonists [6-11].

Midazolam is a water soluble benzodiazepine with rapid onset of action (30-60 seconds with peak effect in 3-5 minutes) and produce both sedation and amnesia. It produces its pharmacologic effect by facilitating the action of Gamma-Amino Butyric Acid (GABA), the principal inhibitory neurotransmitter in the Central Nervous System (CNS). It is rapidly metabolised by hepatic microsomal enzymes to 1-hydroxymidazolam and 4-hydroxymidazolam. These metabolites have an estimated clinical potency of 20-30 % of midazolam and are rapidly conjugated and excreted in the urine. It lacks analgesic properties and must be used with other anesthetic drugs to provide sufficient analgesia. The degree of sedation and the reliable amnesia and preservation of respiratory and hemodynamic function are better overall with benzodiazepines than with other sedative-hypnotic drugs used for conscious sedation. However, the most significant problem with midazolam is respiratory depression [12].

Butorphanol is a synthetic opioid, chemically related to levorphanol, and has mixed agonist-antagonist properties. It is a kappa receptor agonist as well as a mu-receptor antagonist that has ability produce analgesia with limited depression of ventilation with elimination half-life of 2-3 hours. Onset of action is rapid, sedation occurs within 1-2 minutes. Butorphanol is metabolized by hydroxylation and N-dealkylation to form the major metabolite hydroxybutorphanol (45-50% of parenterally administered dose) and norbutorphanol (5-10% of parenterally administered dose). Neither metabolite appears to have any pharmacological effects. It may cause side effects like sedation, nausea, vomiting, dysphoria and respiratory depression [13]. Butorphanol, 20-40 mcg/kg i.v. was comparable or preferable to fentanyl 1-2 mcg/kg i.v. as a supplement to balanced anesthesia [14].

This prospective study was conducted to determine the effectiveness of combination of midazolam and butorphanol for sedation in patients undergoing tympanoplasty under local anaesthesia and to determine satisfaction with sedation technique**.**

Material and Methods:

This study was undertaken at Acharya Vinoba Bhave Rural Hospital attached to Jawaharlal Nehru Medical College, Sawangi (Meghe), Wardha. After institutional ethics committee approval, 100 ASA 1/2 patients of either sex, aged between 18-60 years undergoing tympanoplasty

under local anaesthesia were included in the study after obtaining written informed consent from the patients. Patients with history of motion sickness and allergic reactions to local anaesthetics and study drugs and those prefering general anaesthesia were excluded from the study. All patients had pre-anaesthesia evaluation on a day before surgery and counselled regarding sedation technique, local anaesthesia and operative procedure. The Numerical Rating Scale (NRS 0-10) where 0 indicated no pain and 10 indicated worst pain was explained during preoperative visit. **NRS:** 0: no pain; 1-3: mild pain; 4-7: moderate pain; 8-10: severe pain). On the day of surgery, after confirmation of adequate starvation, intravenous access was secured with 20 G cannula and Ringer's lactate was started. Injection Glycopyrrolate 0.2 mg and injection Ondansetron 4 mg were given intravenously as premedication approximately 15 minutes before taking inside the operation theatre. Monitors such as ECG, NIBP and pulse oximeter were attached to the patient and baseline Heart Rate (HR), arterial Blood Pressure (BP), Respiratory Rate (RR), and Oxygen Saturation (SpO_2) were recorded. Oxygen was administered via nasal cannula at 3 litres/minute. Injection Midazolam 0.03 mg/kg and injection Butorphanol 0.03 mg/ kg was given intravenously followed by midazolam infusion at 0.01 mg/kg/hour. During this period, patients were assessed every 2 minutes using **Ramsay Sedation Score (RSS)** (1=agitated, restless; 2= cooperative, tranquil; 3= responding to verbal commands while sleeping; 4= brisk response to glabellar tap or loud voice while sleeping; 5= sluggish response to glabellar tap or loud voice; 6= no response to glabellar tap). The target end point was the patient having RSS=3. After 5 minutes of the bolus drug injection, if any patient had RSS < 3, an additional bolus injection of intravenous midazolam 0.01 mg/kg and butorphanol 0.01 mg/kg was administered every 5 minutes till RSS=3. Once the RSS=3 was achieved, surgeon was asked to administer local anaesthetic using 2 % lignocaine with adrenaline (1:200000) in postauricular area to block greater auricular, lesser occipital, auriculotemporal nerves and four quadrants of external auditory canal. Patient's response to local anesthetic infiltration was evaluated for pain and body movement. An additional bolus of butorphanol 0.01 mg/kg was given to all those patients responding with the pain score >4 or showing movement during infiltration. Surgery commenced after confirmation of adequate analgesia. Intraoperatively, HR, BP, RR and SpO_2 were recorded every 2 minutes for first 20 minutes and then every 10 minutes till the end of the surgery. Intraoperatively, pain score and sedation score were assessed using NRS and RSS respectively. The total number of additional bolus doses of midazolam and butorphanol were recorded. The midazolam infusion was discontinued at the time of closure, i.e, approximately 15 minutes before the end of surgery**.** At any time, if clinically indicated or if protocol specified maximum amount of additional doses (3 doses) were reached, the sedation technique was converted to alternative sedative or anaesthetic technique. Adverse events like bradycardia, hypotension, hypertension, hypoventilation or desaturation during the surgery were noted and treated accordingly. After the completion of surgery, injection Diclofenac 50-75 mg was given

intramuscularly and patients were shifted to PACU, and monitored for vital parameters (HR, BP, RR, and SpO_2), degree of analgesia and sedation. Postoperatively, surgeons were asked to grade the surgical conditions and their satisfaction with sedation technique on NRS with 0=least satisfied and 10=most satisfied.

Statistical Analysis:

Data analysis was done using SPSS 17.0 version. The inferential statistical analysis was derived using unpaired Student t-test. P value less than 0.05 was considered as significant.

Results:

One hundred patients including 54 male and 46 female patients were involved in the study as shown in Table 1. Ninety six patients belonged to ASA 1 physical status while 4 patients were of ASA 2 status. The mean age was 32.86 ± 10.74 years while mean weight was 51.5 ± 5.63 kg. The mean duration of surgery was 92.7 ± 8.16 minutes. The mean dosage of midazolam required to produce RSS =3 was 1.65 ± 0. 179 mg followed by mean infusion of 0.819 ± 0.089 mg, thus requiring a mean total of 2.45 ± 0.233 mg for sedation. The mean initial bolus dose of butorphanol was 1.562 ± 0.171 mg. Fifteen patients required additional bolus of midazolam and butorphanol of 0.01 mg/kg to produce adequate sedation and analgesia. The total butorphanol dosage required was 1.65 ± 0.179 mg. The peak sedation with combination of midazolam and butorphanol was attained within 4-8 minutes. Only one patient needed conversion to general anaesthesia due to excessive movements and feeling of claustrophobia. No serious side effects such as excessive bradycardia, hypotension or hypertension, excessive hypoventilation and desaturation were observed. The mean surgeon satisfaction score about sedation and patient cooperation for tympanoplasty procedure was 9.8. The distribution of haemodynamic variables as shown in Fig. 1. The distribution of sedation scores and pain scores as shown in Fig. 2.

Table 1: Patient Characteristics and Drug Requirements

Mean Age (Years)	32.86 ±10.74
Mean Weight (Kg)	51.5 ± 5.63
Male : Female distribution	54:46
ASA status distribution	96:04
Mean duration of surgery (minutes)	92.7 ± 8.16
Mean total dose of Midazolam (mg)	2.45 ± 0.233
Mean total dose of Butorphanol (mg)	1.65 ± 0.179

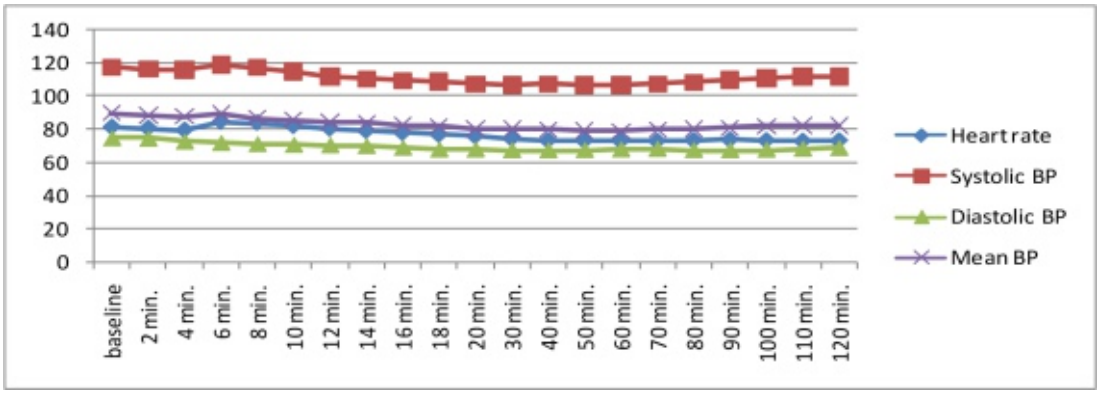

Fig. 1: Distribution of Haemodynamic Variables

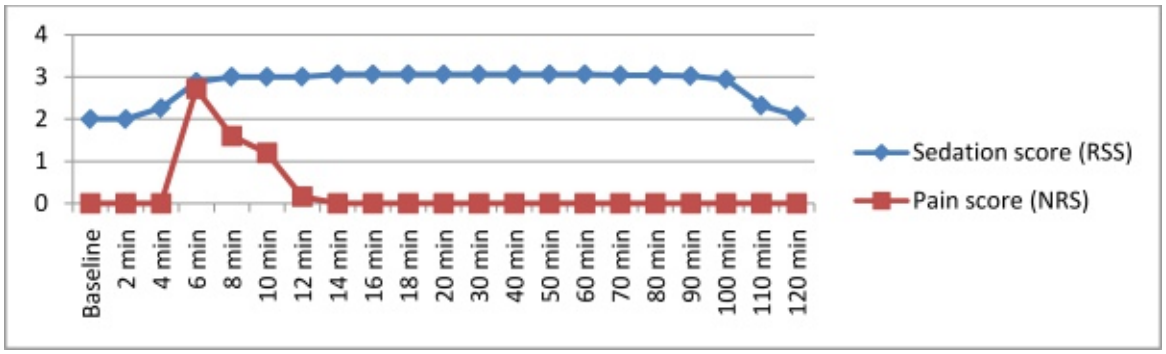

Fig. 2: Distribution of Sedation Scores and Pain Scores

Discussion:

Tympanoplasty is routinely done under local anaesthesia supplemented with intravenous sedation. In ear surgeries, excellent analgesia is achieved by blocking the branches of the great auricular nerve (retroauricular infiltration) and tympanic branch of auriculotemporal nerve (V-shaped infiltration). The mastoid cells are devoid of sensations, so drilling is not painful for the patient. Pain sensation depends not only on the extent of surgical trauma and infiltration technique, but also on the patients' emotional status and previous experiences. Careful explanation of the procedure in the preoperative visit reduces the anxiety.

Several drugs have been used for sedation during tympanoplasty under local anaesthesia with monitored anaesthesia care including Propofol, benzodiazepines, opioids and alpha-2 agonists. Benedik *et al* [7], in a clinical trial stated that both propofol and midazolam can be safely used for sedation in middle ear surgery under local anaesthesia. However, propofol may cause oversedation and disorientation [14]. Also use of propofol has been associated with local anesthetic injection pain, more incidence of breakthrough pain, patient discomfort or patient movement [15-16].

Dexmedetomidine, a new alpha-2 agonist agent, has also been used with success for sedation in middle ear surgery [9, 10], but it proved inferior to midazolam in patients undergoing cataract surgery [17].

We have selected combination of midazolam and butorphanol for sedation for tympanoplasty. Using combination of two agents can provide

better patient control and allows the use of smaller doses of each single agent avoiding its undesirable effects [18]. Midazolam has sedative and anxiolytic activities, provides anterograde amnesia and thus reduces pain perception. Its anxiolytic effect could reduce the emotional component of pain. Butorphanol is a kappa receptor agonist as well as a mu-receptor antagonist, resulting in analgesic and sedative properties without profound respiratory depression or euphoria. These properties make it a potentially useful drug for ambulatory surgical patients [19].

In our study, we used bolus doses of midazolam 0.03 mg/kg and butorphanol 0.03 mg/kg followed by midazolam infusion at 0.01 mg/kg/hour and additional doses of 0.01 mg/kg of both midazolam and butorphanol, if required. The mean dosage of midazolam required to produce RSS=3 was 1.65 ± 0. 179 mg followed by mean infusion of 0.819 ± 0.089 mg, thus requiring a mean total of 2.45 ± 0.233 mg for sedation. The mean initial bolus dose of butorphanol was 1.562 ± 0.171 mg. The total butorphanol dosage required was 1.65 ±0.179 mg. Fifteen patients needed additional doses of 0.01 mg/kg of both midazolam and butorphanol over bolus doses of 0.03 mg/kg to achieve satisfactory sedation and pain scores. The doses of midazolam and butorphanol used in the study were comparable to other similar studies [10, 19-24].

In our study, the mean sedation score of RSS=3 was attained within 4-8 minutes with maximum sedation score of RSS=3.06 from 14-60 minutes. Only 6 patients had sedation score of RSS=4, while 93 patients had sedation score of RSS=3 for the duration of surgery. In similar study conducted by Lippman *et al* [21], butorphanol 2 mg and promethazine 25-50 mg was used for premedication. They observed that the onset time for sedation ranged from 3-25 minutes with mean of 8 minutes and concluded butorphanol with promethazine produced marked sedation and drowsiness in 90 % of patients. Also, the pain score of NRS<3 was achieved within 4-8 minutes and almost all patients perceived the needle pricks of local anaesthetic injection as mild discomfort (NRS=2.82±0.72, P<0.05). All patients were almost painless at incision (NRS=0.36±0.48, P<0.05) and till the end of surgery. In our study, we used NRS for the assessment of pain because patients face remains covered during tympanoplasty and it becomes difficult to assess pain by Visual Analogue Scale (VAS). Hjermstad *et al* [25], compared NRS, Verbal Rating Scale (VRS) and VAS for the assessment of pain intensity in adults and concluded that NRS is applicable for unidimensional assessment of pain intensity in most settings. Ferraz *et al* [26], in their study has observed that NRS has higher reliability in both literate and illiterate patients and thus the NRS is a simple reporting instrument that can help to quantify a patients subjective pain.

The baseline Heart Rate (HR) was 81.32±10.13 /min. There was a slight increase in HR to 84.54±8.97 (P>0.05) during local anaesthetic injection. However, there was slight steady decrease in the HR thereafter to 73.1±6.86 (P<0.05) at 120 minutes. The baseline systolic, diastolic and mean BP were 117.54±7.21 mmHg, 75.12±5.98 mmHg, and 89.48±5.38 mmHg respectively. The systolic BP slightly increased to 119.04±7.2 mmHg (P>0.05) during local anaesthetic injection and thereafter showing slight decrease to 106.9 ±4.28 to 111.92±4.93 mmHg (P<0.05) from 30-120 minutes. However, there was consistent decrease in diastolic BP to 68.96±3.92 mmHg (P<0.05). Mean arterial pressure (MAP) also showed a consistent

decrease from baseline to 80.78±4.63 mmHg (P<0.05). Philip *et al* [19] also have observed a fall in heart rate and diastolic blood pressure with intravenous administration of butorphanol. Mishra *et al* [22] observed that administration of midazolam and butorphanol 5 minutes before induction of GA produced a statistically significant fall in HR and MABP attributed to anxiolysis and synergistic sedative effects of midazolam and butorphanol. The hemodynamic changes in our study were similar to other studies [23, 24, 27].

None of the patients had significant respiratory depression as manifested by hypoventilation (respiratory rate <10 breaths/minute) or desaturation (SpO_2 <94%). Because of its antagonist action on mu- receptors, butorphanol results in low incidence of respiratory depression. Other studies comparing butorphanol also observed no significant respiratory depression with butorphanol [28-29].

The study demonstrated that the operating surgeons were highly satisfied with the sedation technique (satisfaction score=9.8) attributed to the relatively stable heart rate and lower MAP resulting a clear operating field, no patient movements and complaints of pain and high compliance of patients with sedation technique.

Conclusion:

Thus, combination of midazolam 0.04-0.05 mg/kg and butorphanol 0.03-0.04 mg/kg in association with effective local anaesthetic infiltration produces adequate anaesthesia for tympanoplasty under monitored anaesthesia care. The analgesic and sedative properties of butorphanol helps to reduce the requirement and the associated side effects of midazolam.

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