International Journal of Medical Anesthesiology

E-ISSN: 2664-3774
P-ISSN: 2664-3766
www.anesthesiologypaper.com
IJMA 2020; 3(1): 91-95
Received: 08-11-2019
Accepted: 11-12-2019

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Comparative study of dexmedetomidine versus midazolam in monitored anaesthesia care in tympanoplasty surgery

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DOI: https://doi.org/10.33545/26643766.2020.v3.i1b.73

Abstract
Background: Monitored anaesthesia care (MAC) has become increasingly used for middle ear surgeries. Midazolam is most commonly used for sedation in MAC; likewise, dexmedetomidine has gained popularity for intravenous sedation for the procedures to be done under MAC. The present study was undertaken to evaluate and compare the perioperative effects of inj. dexmedetomidine and midazolam with respect to sedation, analgesia and hemodynamic stability.
Method: Study was approved by the Institutional Medical Ethics Committee and written informed consent was obtained from all patients participating in the study. Total 60 patients of ASA Grade I and II, aged 18 - 60 years, undergoing tympanoplasty surgery under local anaesthesia with 2% Lignocaine plus adrenaline 1:200000 and sedation with infusion of either dexmedetomidine or midazolam drug. Patients were divided in two groups of 30 patients in each group by chit block method. Group D received Dexmedetomidine 1 mcg/kg IV bolus over 10 min followed by continuous IV infusion at 0.5 mcg/kg/hr. Group M received midazolam 40 mcg/kg IV over 10 min followed by continuous IV infusion at 20 mcg/kg/hr.
Results: Perioperatively, sedative effects of dexmedetomidine and midazolam were almost comparable, analgesic effects of dexmedetomidine was better than midazolam IV infusion. The significant reduction in haemodynamic variables was noted with dexmedetomidine (p=0.001) provided better hemodynamic stability than midazolam. Oxygen saturation and respiratory rate were maintained within normal limits in both the groups. 80% of surgeons in either group showed significant satisfaction but the difference was not statistically significant between two groups.
Conclusion: Dexmedetomidine is a safe agent as sedative in patients undergoing tympanoplasty surgery under local anaesthesia with MAC.

Keywords: Midazolam, sedation, dexmedetomidine, tympanoplasty, lignocaine, adrenaline, bradycardia

Introduction
Tympanoplasty is an ear surgery which involves reconstruction of perforated tympanic membrane with or without ossicular reconstruction. It is superficial, less invasive surgery and can be done under local anaesthesia with or without sedation under monitored anaesthesia care (MAC) in cooperative and well counseled patients [1]. This technique of local anaesthesia with sedation has various advantages such as less bleeding, cost-effectiveness, postoperative analgesia, faster recovery and ability to test hearing intraoperatively [2].
Several drugs have been used for sedation during surgery under local anesthesia with MAC including propofol, benzodiazepines, opioids and α2 agonists either alone or in combination [3, 4]. Midazolam is a potent imidazobenzodiazepine which possesses typical benzodiazepine properties namely hypnotic, amnestic, anticonvulsant and anxiolytic activity. Midazolam is the most frequently used sedative and has been reported to be well tolerated when used in MAC [5]. However, it has a number of beneficial effects when used for sedation, fast onset, and limited duration of action. Despite having a number of beneficial effects, it can cause prolonged sedation and respiratory depression after repeated administration of bolus doses [6].
To overcome these untoward side effects of midazolam new drugs, such as the α2-agonists i.e. Dexmedetomidine, have emerged as alternatives for IV sedation. Dexmedetomidine offers beneficial pharmacological properties producing sedation, analgesia, and anxiolysis without relevant respiratory depression, [7] along with shorter half-life and wider margin of safety which makes it a suitable agent to be used for procedures under MAC [1]. Also, it

decreases sympathetic outflow and hence, has been reported to reduce bleeding significantly in ENT surgeries. Thus, in present study, we used compared intravenous infusion of dexmedetomidine and midazolam to evaluate and compare the effects of each drug in respect to sedation, analgesia and hemodynamic stability intraoperatively and postoperatively in patients undergoing tympanoplasty surgery under local anaesthesia with MAC.

Materials and Methods

The present prospective, randomized, double blind, comparative study was conducted in 60 patients of either sex aged between 18-60 years of ASA grade I and II undergoing tympanoplasty surgery under local anaesthesia with MAC. Study was approved by the Institutional Medical Ethics Committee and written informed consent was obtained from all patients participating in the study. Patients with asthma, myocardial infarction in last 6 months, arterial fibrillation, heart blocks, raised serum urea and creatinine, advanced liver disease (liver enzymes twice the normal range or higher), history of chronic use of sedatives, narcotics and alcohol, known sensitivity to local anaesthesia drug lignocaine, allergy to any of the study drugs, patients on beta blocker drugs, pregnant and lactating women were excluded from the study. All the selected patients were randomly allocated in two groups of 30 patients in each group by chit block method to receive either Injection dexmedetomidine (Group D) or Injection midazolam (Group M) for sedation during surgery.

The day before surgery, all the patients were examined and thoroughly investigated according to institute protocol and kept fasting overnight. On the day of surgery, patient was taken on operation table. Standard monitoring including ECG, noninvasive BP and pulse oximetry were applied to patients and baseline vitals were recorded. IV line was secured with 20G cannula, antiemetic premedication drug i.e. Ondensetron 0.15 mg/kg IV was injected and IV Ringer Lactate solution at 2ml/kg/hr was started. O2 was administered with nasal canula at 2lit/min. To maintain the double-blind nature of study, anesthesiologist who was not involved in study prepared the drug infusions to fixed volume i.e. 20 ml for loading dose and 25 ml for maintained infusion. The anesthesiologists conducting the case, surgeon and the patient were blinded to group assignment. Patients in group D received Inj. dexmedetomidine 1 mcg/kg IV bolus over 10 min followed by continuous infusion at 0.5 mcg/kg/hr while patients in group M received Inj. midazolam 40 mcg/kg IV over 10 min followed by continuous infusion at 20 mcg/kg/hr. Loading dose of both the drugs were calculated and diluted to 20ml with 0.9% normal saline and kept at constant rate of 120ml/hr given over 10 min. After the loading dose of the drug, Ramsay Sedation Score (RSS) was assessed with target sedation of RSS 3. Infusion was stopped when RSS was 3 or full 20ml bolus had been given whichever was earlier. If the RSS<3 at the end of 10 min of loading dose, patients were given Inj propofol 100-300mcg/kg IV bolus as a common rescue sedative in both the groups. The protocol specified up to a maximum of 2 rescue doses. RSS was assessed throughout the duration of surgery and in postoperative period every 15 min till 120 min. Once RSS was 3, local anaesthesia was given by the operating surgeon, using lidocaine 2% with adrenaline 1:200,000, 6-7 ml. The maintenance infusion was commenced at constant infusion rate for both the groups, according to weight of patient. Group D: Inj. dexmedetomidine infusion was prepared by adding 100 mcg in 25 ml of 0.9% normal saline containing 4mcg/ml at 0.5 mcg/kg/hr and group M: Inj. midazolam infusion was prepared by adding 4 mg in 25 ml of normal saline containing 0.16mg/ml at20 mcg/kg/hr.

Intraoperative pain intensity was assessed with VAS (0-10). If VAS >3 OR whenever patient complained of pain during surgery, Inj. Fentanyl at 1 mcg/kg was given as rescue analgesic and additional dose of local anaesthetic 2-3 ml (not exceeding the maximum dose) was repeated by surgeon if required. The maintained infusions were discontinued approximately 15 minutes before the end of surgery. Heart rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean arterial pressure(MAP), Respiratory Rate(RR), Oxygen Saturation(SpO2) were recorded at the start of loading infusion, 5 min after, at the end of loading infusion and every 15mins thereafter till the end of surgery and postoperatively for 2 hours. At any time, if clinically indicated or if protocol specified amounts of rescue drugs were given, the technique was converted to any alternative sedative or anesthetic therapy and the study drug was discontinued. Such incidents were noted and the subjects were withdrawn from further analysis.

After completion of surgery patients were shifted to Post Anaesthesia Care Unit (PACU) and were monitored for hemodynamic parameters. Postoperative pain was assessed using VAS (0-10). If VAS >3, analgesia was provided with IV Inj Diclofenac 1.5mg/kg. The surgeons were asked to rate their satisfaction with operating conditions, using 5-point Likert scale at the end of surgery, acceptable satisfaction score of surgeons being 4 and 5. Adverse effects namely Bradycardia, Hypotension, Hypertension, desaturation, nausea, vomiting, dry mouth or any other events during procedure and postoperatively for 2 hours were noted and treated accordingly.

Statistical Analysis

Data was expressed as Mean ± Standard Deviation (SD). Demographic data and complications were analyzed using Chi-square test and haemodynamic variables were analyzed using paired and unpaired ‘t’ test. ‘P’ value less than 0.05 was considered statistically significant.

Observations and Results

There was no statistically significant difference found between two groups with respect to demographic profile and mean duration of surgery. Hence both the groups were comparable as shown in table 1.

Table 1: Demographic profile and mean duration of surgery

Parameters		Group D	Group M	P Value
Age (Years)		32.33±10.40	31.77±12.92	0.853
Weight (kg)		57.73±7.83	55.7±7.08	0.130
Sex	Male	18 (60%)	18 (60%)	1.000
	Female	12 (40%)	12 (40%)	(NS)
ASA	I	26 (86.7%)	25 (83.3%)	0.717
	II	04 (13.3%)	05 (16.67%)	(NS)
Duration of surgery (min)		89.50 ± 13.35	89.00 ± 16.21	0.896 (NS)

Intraoperative, RSS at the end of 10 min was 3.03 ± 0.31 in group D and 2.86 ± 0.34 in group M. But the difference was not statistically significant. There was statistically

significant difference between RSS among the two groups at 15 min and 30 min duration during the surgical time. The difference was not statistically significant at the end of 10 mins, 45 mins, 60 min and 75 min, (Figure 1).

In group D only 1 (3.33%) patient and in group M, 4 (13.33%) patients required additional sedative, once only but the difference was not statistically significant, (P value=0.1611).

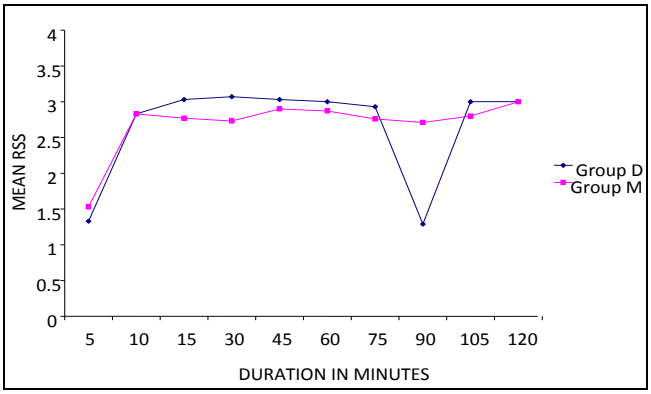

Fig 1: Intraoperative changes in mean RSS in both the groups

Figure 2 show RSS among the two groups in postoperative period. Mean RSS at arrival was 1.97 in group D and 2.38 in group M. The difference was statistically significant until 30 min and again at 75 min. There was no statistically significant difference between RSS of two groups otherwise.

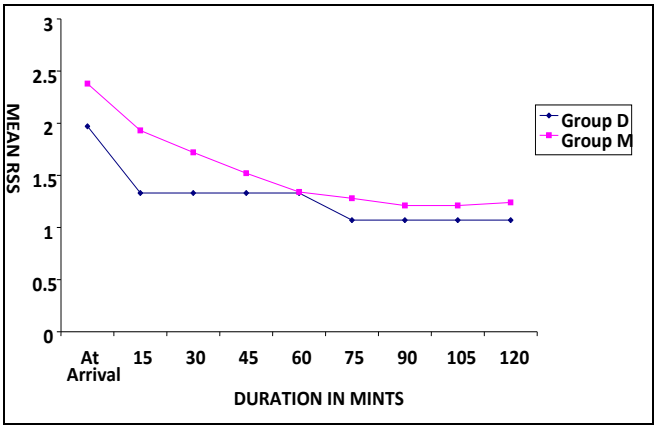

Fig 2: Postoperative mean RSS in both the groups

The VAS score was higher in group M with statistically significant difference from 15 minutes onwards throughout the duration of surgery except at 120 min, (Figure 3). In group D, 2 patients required additional analgesia once at 30 min and 60 min. In group M, 6 patients required additional analgesic, out of which 3 patients required it at 30 min, 2 patients at 45 min and 1 patient each at 60 min and 105 min duration intraoperatively, (p=0.128).

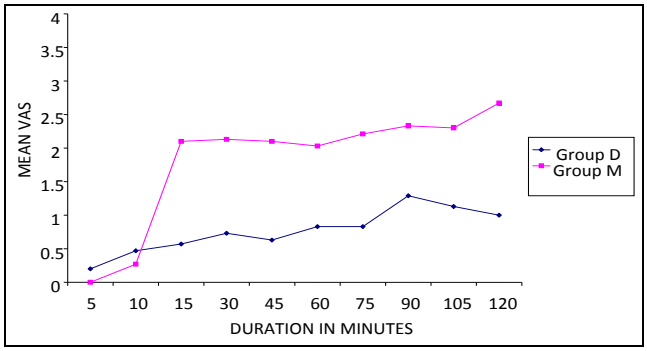

Fig 3: Visual Analogue Scale in two groups intraoperatively

Postoperatively, mean VAS was significantly lower in group D than group M throughout duration of 120 min, as shown in figure 4. In group D, only one (3.3%) and in group M, four (13.33%) patients required additional analgesia at different times postoperatively and difference between two groups was not statistically significant.

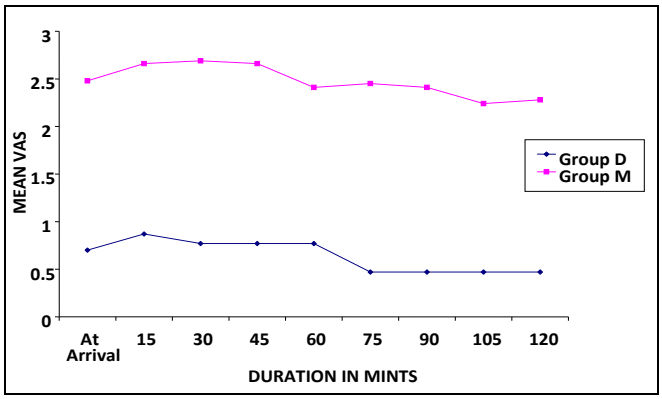

Fig 4: Visual Analogue Scale in two groups post-operatively

Intra-operatively, the baseline haemodynamic parameters (HR, SBP, DBP and MAP) were comparable between two groups. With group D fall in mean HR was more than the group M throughout the duration of surgery, (p=0.002). The reduction in SBP was significantly lower in group D than in group M. So fall in DBP was significantly more in group D than in group M. MAP was significantly lower in group D than in group M till the end of surgery, except at 120 minutes. Baseline SpO2 in group D was 99.47% and in group M was 99.07%. The difference between two groups was not statistically significant throughout the duration of surgery. There was significant fall in respiratory rate (RR) among group M patients compared to group D and the difference was statistically significant throughout the duration of surgery, but RR was within normal limit (RR>8). Thus patients in midazolam group showed respiratory depression with reduced respiratory rate.

In PACU, haemodynamic parameters (HR, SBP, DBP and MAP) were significantly lower in group D than in group M for 2 hours. Thus, the significant reduction in

haemodynamic variables was noted with dexmedetomidine, (p=0.001). There was no fall in SpO2 in either group and data was statistically not significant. Mean respiratory rate at arrival was comparable between two groups with no significant difference throughout the period of 2 hours.

Overall 80% of surgeons in either group showed significant satisfaction but the difference was not statistically significant among both the groups as shown in table 2. There was a single incidence of bradycardia and hypotension in group D whereas no side effects noted in group M.

Table 2: Surgeon Satisfaction Score

Score	Proportion of cases with Surgeon satisfaction			
	Group D		Group M	
	No.	%	No.	%
1	-	-	-	-
2	-	-	-	-
3	06	20.0	06	20.0
4	15	50.0	15	50.0
5	09	30.0	09	30.0
Total	30	100.0	30	100.0

Discussion

Dexmedetomidine is a novel drug for patients being operated under monitored anaesthesia care. It provides appropriate anaesthesia and analgesia intraoperative and postoperative period. Hypotension and bradycardia have been observed in studies done earlier with dexmedetomidine [8, 9]. These effects are known to be related to the dose, route of administration, and infusion rate (in intravenous administrations) [10-12]. Reports of its use state that alpha-2 agonist effect is observed, but not alpha-1 effect, on administration of low and moderate doses and slow rates of infusion. Consequently, peripheral vasoconstriction and hypertension would not be expected in these instances [13, 14]. Taking these data into account, we elected to use it in a dosage of 1 μg/kg, so as to avoid side effects associated with high infusion rates.

The present study found significantly more sedation with dexmedetomidine than midazolam infusion during the surgical procedure up to 30 minutes duration but thereafter it was comparable in both the groups. The mean RSS was significantly higher at almost all-time intervals in group D, implies that the level of sedation was found to be significantly better with dexmedetomidine. This result correlated well with the study done by Parikh *et al.* [4] and Mohamed *et al.* [15] The rescue sedation with propofol was required for one patient in group D and 4 patients in group M, but it was not statistically significant. The sedative effect of dexmedetomidine and midazolam was comparable at the end of loading dose, at 10 minutes and also after 30 min till the end of surgery. Also, we found lower RSS in group D than in group M postoperatively, suggesting better recovery from sedation by dexmedetomidine than midazolam. These findings are similar to the study done by Candiotti *et al.* [3] and Turan *et al.* [16]

In perioperative period VAS score was found to be lower in group D when compared to group M with reduced requirement of rescue analgesics (Inj. Fentanyl IV intraoperatively and Inj. Diclofenac IV postoperatively) which is concordance with previous studies [12, 16-18] suggesting analgesic effect of dexmedetomidine was better than midazolam in perioperative period in patients undergoing surgery with LA and MAC.

When compared with midazolam, dexmedetomidine-induced bradycardia was not statistically significant and was not found to be clinically challenging. Similar observations were reported by Dyck and colleagues [19] and Erkola and colleagues [20]. The present study found significant reduction in haemodynamics in group D compared with baseline values and corresponding values in group M, intra and postoperatively. This is correlated with the other studies [7, 21]. suggesting that dexmedetomidine and midazolam both produce stable haemodynamics. It leads to depressive effects on hemodynamic parameters at the loading dose of 1 μg/kg over 10 min, but this effect does not reach the level of severe impairment as shown by Eren *et al.* [22] The HR, SBP, DBP, MAP were lower in group D with clinical advantage over midazolam in providing better operative field for microscopic surgery [4].

The respiratory rate shows significant reduction in group M patients compared to group D perioperatively, but was within normal limits (RR >8/min) suggesting that there is no respiratory depression in dexmedetomidine group compared to midazolam group. SpO2 was maintained within normal limits in both the groups. These results are correlated well with the earlier studies [22, 23].

Parikh *et al.* [4] and Vyas [5] and demonstrated significant higher surgeon's satisfaction score in group D than in group M in their studies. But in present study, the surgeon satisfaction score of 4-5 was achieved among 80.0% of surgeons in both the groups. No patients had any episode of hypertension, desaturation, respiratory depression, nausea, vomiting or dryness of mouth. Only one patient had an episode of bradycardia in dexmedetomidine group, which was treated by giving Inj. Atropine 0.6 mg IV and one patient had hypotension which was treated with IV fluid replacement and Inj. Ephedrine 5mg IV in incremental doses.

Conclusion

From the result of present study, it can be concluded that, intravenous infusion of Dexmedetomidine causes better sedation, lower VAS scores and reduces requirement of rescue analgesia by virtue of its analgesic and sedative effect. Dexmedetomidine also provides better hemodynamic stability than midazolam. It leads to depressive effects on hemodynamic parameters at the dose of 1 μg/kg, but this effect does not reach the level of severe impairment. It may be suggested that its use normalizes increased blood pressure and HR due to peri-operative anxiety. Its effects on respiratory parameters are definitely less than midazolam.

Thus, dexmedetomidine is a safe agent as sedative in patients undergoing tympanoplasty surgery under local anaesthesia with monitored anaesthesia care. It provides a calm patient, better intra- and post-operative analgesia and better surgical field in ASA I/II patients. However, more studies are needed to focus on its effects on debilitated patients.

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