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Research Article

Comparative study between dexmedetomidine/nalbuphine and midazolam/nalbuphine in monitored anesthesia care during ear surgery

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KEYWORDS

Dexmedetomidine;
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Monitored anesthesia care;
Ear surgery

Abstract *Background:* Monitored anesthesia care (MAC) is the practice of administrating local anesthesia in combination with IV sedatives, anxiolytics and/or analgesic drugs during certain surgical procedures. Most of ear surgeries can be done under monitored anesthesia care.
Methodology: This is a randomized, double blind, prospective study and 100 patients undergoing ear surgery under MAC were divided into two groups of 50 patients each. The patients in group (*D*) received dexmedetomidine 1 μg/kg IV over 10 min followed by 0.7 μg/kg/h + nalbuphine 100 μg/kg IV and in group (*M*) received midazolam 20 μg/kg IV followed by 20 μg/kg/h + nalbuphine 100 μg/kg over 10 min. Assessment of sedation by Ramsay sedation score, requirement of intraoperative rescue sedation, intraoperative VAS, intraoperative rescue analgesia, intraoperative hemodynamics, intraoperative bleeding, intraoperative complications, postoperative visual analogue score and postoperative rescue analgesia requirement, time to achieve full recovery and satisfaction scores of patients and surgeon were recorded.
Results: Group (*D*) showed more sedation by Ramsay sedation score than the midazolam (*M*) group. Fifty percent in group (*M*) needed more rescue sedation than 26% in group (*D*) ($p < 0.05$). Intraoperative VAS was significantly higher in group (*M*) than in group (*D*) that led to the use of more rescue analgesia in 60% of group (*M*). Intraoperative heart rate and mean blood pressure were significantly lower in group (*D*) than in group (*M*) ($p < 0.05$). There was no statistical difference between the two groups as regards respiratory rate or SpO_2. Intraoperative bleeding is less significantly less in group

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(*D*). Intraoperative hypotension was significantly higher in group (*D*) (30%) than in group (*M*) (20%). Bradycardia was insignificantly higher in group (*D*). As regards postoperative VAS, group (*D*) was significantly lower than group (*M*). This led to the use of more rescue analgesia in 94% of group (*M*). There was no statistically significant difference between the two groups as regards recovery time. Patient's satisfaction was significantly higher in group (*D*) (80%) compared with group (*M*) (60%) ($p > 0.05$). The same as regards doctor's satisfaction where satisfaction was significantly higher in group (*D*) (76%) than in group (*M*) (54%).

Conclusion: We concluded that the combination of dexmedetomidine/nalbuphine is a better alternative to midazolam/nalbuphine in MAC since it provides analgesia, amnesia and sedation with better intraoperative and postoperative patient satisfaction with better surgical field exposure.

1. Introduction

According to the American Society of Anesthesiologists (ASA), a monitored anesthesia care (MAC) is a planned surgical procedure during which surgery is performed under local anesthesia together with sedation and analgesia [1]. The 3 essential elements and purposes of a conscious sedation during a MAC are as follows: safe sedation, control of the patient anxiety and analgesia [2]. Most of ear surgeries can be done under monitored anesthesia care. It is essential for such delicate procedures to have a bloodless surgical field which can be provided by the addition of vasoconstrictor agent (usually epinephrine) to the local anesthetic infiltration and avoiding pain and anxiety [3].

Drugs that can be used during monitored anesthesia care should be chosen according to the type and time of surgical procedure, patient's medical and psychological conditions and experience of the anesthetic team [4]. Many drugs can be used for sedation during surgery under local anesthesia with monitored anesthesia care including opioids, benzodiazepines and propofol [5]. However, propofol may cause respiratory embarrassment [6]. Benzodiazepines may result in confusion and subsequent agitation, particularly in old age [7] and opioids are associated with increased risk of respiratory depression and oxygen desaturation [8]. 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.

Midazolam is a benzodiazepine which has sedative and anxiolytic activities, provides anterograde amnesia, and has anticonvulsant properties [9].

Alpha-2 adrenoreceptors agonists i.e. clonidine and dexmedetomidine are increasingly used for their sedative, analgesic, sympatholytic and cardiovascular stabilizing effects [10].

Nalbuphine is an agonist–antagonist opioid that is structurally related to oxymorphone and naloxone. Autoradiography studies indicate that nalbuphine binds to μ receptors as well as to $\hat{e}$ and $\ddot{a}$ receptors. Nalbuphine acts as an antagonist at the μ receptor and an agonist at the $\hat{e}$ receptor. Activation of supraspinal and spinal μ receptors results in limited analgesia, respiratory depression, and sedation [11].

2. Patients and methods

The study was conducted in Ain Shams University hospitals at the ENT surgical department. After institutional Ethics Committee approval, informed written consent was taken from each patient included. This study was designed as a randomized, double blind clinical trial.

Patients who were scheduled for elective ear surgeries under local anesthesia like tympanoplasty, myringoplasty or stapedectomies were included in this study. Exclusion criteria were hypertension, renal impairment, advanced liver disease, history of alcohol or drug abuse, or allergy to any of the study medications. Using a computer-generated program, 100 patients were randomly divided into two groups of 50 patients each to receive either dexmedetomidine/nalbuphine (group (*D*)) or midazolam/nalbuphine (group (*M*)) for sedation and analgesia during surgery. To follow the double blind nature of the study, drugs were prepared by an independent anesthesia technician and diluted to a fixed volume for every single drug used. The anesthesiologist who attended the surgery and recorded the data was also blind to both groups assigned.

Baseline heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR), peripheral oxygen saturation (SpO_2) values were obtained using standard monitors. Intravenous cannula 22 gauge was inserted. Group (*D*) patients received dexmedetomidine 1 μg/kg IV over 10 min followed by 0.7 μg/kg/h + nalbuphine 100 μg/kg IV and group (*M*) patients received midazolam 20 μg/kg IV over 10 min followed by 20 μg/kg/h + nalbuphine 100 μg/kg. Local anesthetic infiltration was given by the operating surgeon, who was unaware of the group allocation, using lidocaine 1% with adrenaline 1:200,000. Paracetamol infusion 1gm was given to all patients.

After that, level of sedation was assessed using Ramsay Sedation Score (RSS). The desired sedation level was defined as RSS $\geqslant 3$. If RSS was less than 3, rescue sedation with propofol 100–200 μg/kg/h IV was given. Then surgeon proceeded to perform the surgery under local anesthesia. Intraoperative visual analogue scale (VAS) was measured. Whenever patient complained of pain during the surgery, the surgeon used an additional dose of local anesthetic.

Heart rate (HR), mean arterial pressure (MAP), respiratory rate(RR), and peripheral oxygen saturation (SpO_2) were recorded every 10 min till 60 min. Intraoperative bleeding was assessed by bleeding scale (0–4), acceptable bleeding score being 0–2, if bleeding score > 2 propofol was given.

All adverse events like bradycardia (HR < 55 beats/min), hypotension (MAP < 50 mmHg sustained for > 10 min), respiratory depression (respiratory rate < 10 bpm), oxygen desaturation ($SpO_2 < 90\%$), nausea or vomiting were recorded.

After completion of the surgery patients were transferred to the recovery room where the following were done:

- Assessment of postoperative pain using Visual Analogue Scale (0–10 cm); if VAS was > 3, analgesia was provided with intravenous tramadol 0.5–1 mg/kg.

- Assessment of Aldrete score in the recovery room every 5 mines, till score of 10 was achieved. Time to achieve Aldrete score of 10 was recorded, which was the time to shift the patient to the ward.
- Assessment of patient's satisfaction was done by asking the patient to answer the question, "How would you rate your experience during surgery?" using a 7-point Likert verbal rating scale. This assessment of patient's satisfaction was performed just before shifting to ward to minimize the effects of sedation on patient's judgment.
- Surgeons were also asked to rate their satisfaction with operative conditions, using the 7-point Likert verbal rating scale at the end of surgery, acceptable satisfaction score of both the patient and surgeon being 5–7.

2.1. Various scores used in the study

2.1.1. Sedation scale (Ramsay Sedation Scale) is as follows:

1. Anxious, agitated or restless.
2. Cooperative, oriented and tranquil.
3. Responds to command.
4. Asleep but has a brisk response to light glabellar tap or loud auditory stimulus.
5. Asleep has a sluggish response to a light glabellar tap or loud auditory stimulus.
6. Asleep no response.

2.1.2. Intraoperative bleeding scale

0-No bleeding.
1-Slight bleeding; no suctioning of blood required.
2-Slight bleeding; occasional suctioning required. Surgical field not threatened.
3-Slight bleeding; frequent suctioning required. Bleeding threatened surgical field a few seconds after suction was removed.
4-Moderate bleeding; frequent suctioning required. Bleeding threatened surgical field directly after suction was removed.

2.1.3. Likert scale

1	2	3	4	5	6	7
Extremely dissatisfied	Dissatisfied	Somewhat dissatisfied	Undecided	Somewhat satisfied	Satisfied	Extremely satisfied

2.1.4. Postanesthesia recovery score (Modified Aldrete Score)

Parameter	Score		
	2	1	0
Activity	Moves all extremities voluntarily or on command	Moves two extremities voluntarily or on command	Unable to move extremities
Respiration	Breathes deeply and coughs freely	Dyspnea, shallow or limited breathing	Apneic
Circulation	BP ± 20 mm of preanesthetic level	Bp ± 20–50 mm of preanesthetic level	BP ± 50 mm of preanesthetic level
Consciousness	Fully awake	Arousable on calling	Not responding
Oxygen saturation	SpO_2 >92% on room air	Supplemental O_2 required to maintain SpO_2 >90%	SpO_2 <90% with O_2 supplementation
Total score = 10; A score of ⩾9 required for discharge			

2.1.5. Visual Analogue Scale VAS (0–10cm)

0	2	4	6	8	10
No pain					Worst pain

Data analysis was made by using SPSS 18.0 for Windows. It was estimated that a sample size of 50 patients per group would achieve a power of 90% with type I error 0.05. The test statistic used was the two-sided unpaired *t*-test and the type I error was set at 0.05. Comparison between the two groups as regards numerical variables was made by using Student's *t*-test for comparing means and standard deviation (quantitative data) and Chi-square test for non-numerical variables (qualitative data). Significant results were defined when the *p*-value was less than 0.05.

3. Results

The demographic data of the two study groups are summarized in Table 1. Statistical analysis revealed non-significant differences between the two study groups as regards age, sex distribution, weight and duration of surgery. The surgical procedure performed in patients was either: myringoplasty, tympanoplasty, or stapedectomy. The distribution of these procedures between the two study groups was found to be non-significantly ($p > 0.05$) different between the study groups.

Intraoperative sedation was measured by using Ramsay sedation score. It revealed that there was statistically significant difference between the two studied groups, where the dexmedetomidine (*D*) group (4.254 ± 1.054) showed more sedation than the midazolam (*M*) group (3.548 ± 1.577). This result led to statistically significant difference between the two groups as regards the use of rescue sedation where group (*M*) 25 patients (50%) while group (*D*) 13 (26%) patients needed propofol infusion ($p < 0.05$). Total dose of propofol needed as rescue sedation was statistically significant less in group (*D*) than in group (*M*). Table 2.

Intraoperative pain was measured by using visual analogue scale (VAS). It showed that there was statistically significant difference between the two studied groups, where the VAS was less in group (*D*) (3.87 ± 1.112) than in group (*M*) (5.87 ± 1.874). This result led to statistically significant

Table 1 Demographic data of the two study groups.

	D (*n* = 50)	*M* (*n* = 50)	Test	
			t	*P*-value
Age (year) (Mean ± SD)	34.14 ± 7.54	32.5 ± 6.87	1.13	0.2584
Weight (kg) (Mean ± SD)	79.564 ± 15.156	75.478 ± 17.654	1.242	0.217
Duration of surgery (min) (Mean ± SD)	55.7 ± 10.7465	53.457 ± 9.787	1.091	0.277
Sex N (%)				
Male	30(60%)	28(56%)	1.963	0.1612
Female	20(40%)	22(44%)		
Type of surgery N (%)				
Myringoplasty	12(24%)	15(30%)	0.477	0.7880
Tympanoplasty	20(40%)	19(38%)		
Stapedectomy	18(36%)	16(32%)		

Table 2 Intraoperative variables.

Intraoperative	*D* (*n* = 50)	*M* (*n* = 50)	*T*-test	
			t	*P*-value
Sedation score	4.254 ± 1.054	2.75 ± 0.95	7.49	< 0.001*
Intraoperative rescue sedation (if RSS = 1, 2) *n*(%)	13(26%)	25(50%)	5.136	0.023*
Propofol dose (mg)	140.52 ± 23.12	255.14 ± 30.24	21.292	< 0.001*
VAS	3.87 ± 1.112	5.87 ± 1.874	6.494	< 0.001*
Intraoperative rescue analgesic (if VAS > 3) *n*(%)	17(34%)	30(60%)	5.781	0.016*
Intraoperative bleeding (0–2)	39(78%)	29(58%)	3.722	0.05*

difference between the two groups as regards the use of rescue analgesic drug if VAS > 3 where 30 patients in group (*M*) (60%) and 17 patients in group (*D*) (34%) needed paracetamol infusion ($p < 0.05$). Table 2.

Intraoperative bleeding measured by bleeding scale was statistically significant less in group (*D*) than in group (*M*). Bleeding scale (0–2) was 78% in group (*D*) while in group (*M*) it was 58% ($p < 0.05$). Table 2.

Intraoperative hemodynamics (heart rate, mean blood pressure, respiratory rate, and SpO_2) were measured every 10 min for 60 min. Heart rate and mean blood pressure were statistically significant lower in group (*D*) than in group (*M*) after 10 min from the start to the end of the procedure ($p > 0.05$). Respiratory rate and, SpO_2 were statistically insignificant throughout all the procedure ($p > 0.05$). Table 3.

As regards intraoperative complications 20% of patients in group (*D*) had bradycardia (HR < 55) in comparison with 12% of patients in group (*M*) showing statistically insignificant difference between them ($p > 0.05$). In mean blood pressure there was statistically significant difference between the two studied groups where 15 patients (30%) in group (*D*) had hypotension (MAP < 50 mmHg) while 5 patients (10%) only in group (*M*) had hypotension ($p > 0.05$). There was no significant difference between the two groups as regards nausea and vomiting ($p > 0.05$). No cases had respiratory rate < 10 per minute or $SpO_2 < 90\%$. Table 4.

Postoperative VAS was measured and there was highly statistically significance between the two groups where group (*D*) (4.51 ± 1.77) was less than group (*M*) (6.54 ± 1.87) ($p < 0.05$). This result led to statistically significant difference between the two groups as regards the use of rescue analgesic drug if VAS > 3 where 47 patients in group (*M*) (94%) and 32 patients in group (*D*) (64%) needed tramadol injection ($p < 0.05$). Table 5.

There was no statistically significant difference between the two groups as regards the recovery time. Time to achieve score 10 in Aldrete score was (12.54 ± 2.054) in group (*D*) in comparison with (11.879 ± 1.987) in group (*M*) ($p > 0.05$). Table 5.

Patient's satisfaction was significantly higher in group (*D*) (80%) compared with group (*M*) (60%) ($p < 0.05$). The same as regards doctor's satisfaction where satisfaction was significantly higher in group (*D*) (76%) than in group (*M*) (54%) ($P > 0.05$). Table 5.

4. Discussion

One of the most valuable developments in health care delivery is the shift from inpatient to outpatient surgery and the associated day-case anesthesia. The main benefit for this change is the economic savings afforded by not admitting patients the night before surgery or keeping them in hospital the night after surgery. Other advantages of outpatient surgery include earlier ambulation, better patient convenience, and a lower risk of nosocomial infection [12]. Essential characteristics for agents of day-case anesthesia are early discharge and cost effectiveness [13]. One of the methods of outpatient anesthesia is Monitored Anesthesia Care (MAC) which is a technique of combining local anesthesia with parenteral drugs for sedation and analgesia.

Using single agent for MAC usually does not provide full control of the patient's status and almost always requires intraoperative intervention with rescue medications. So, combining

Table 3 Intraoperative hemodynamics.

		D		M		T-test	
		Mean	SD	Mean	SD	t	P-value
Heart rate (bpm)	T0	91.15	±5.654	90.754	±4.879	−0.375	0.709
	T1	65.15	±3.54	76.48	±4.5	13.990	<0.001*
	T2	60.254	±5.465	70.354	±5.245	9.428	<0.001*
	T3	60.42	±5.0589	68.4	±3.875	8.855	<0.001*
	T4	59.48	±2.23	69.79	±3.87	16.330	<0.001*
	T5	61.125	±3.458	68.787	±4.254	9.883	<0.001*
Mean arterial pressure (mmHg)	T0	85.564	±5.44	87.564	±6.185	1.717	0.089
	T1	73.56	±3.5	87.34	±5.56	14.831	0.000*
	T2	70.165	±5.89	85.3465	±5.89	12.880	0.000*
	T3	70.05	±4.99	80.654	±4.4	11.271	0.000*
	T4	65.87	6.87	78.54	±4.546	10.872	0.000*
	T5	60.58	±6.58	75.54	±3.654	14.055	0.000*
Respiratory rate (pm)	T0	18.56	±1.564	18.46	±1.09	−0.371	0.712
	T1	17.65	±1.335	18.089	±1.216	1.719	0.089
	T2	18.65	±1.056	18.13	±1.8	−1.762	0.081
	T3	17.998	±1.6	17.556	±0.8749	−1.714	0.090
	T4	17.5	±1.115	17.223	±0.95	−1.337	0.184
	T5	17.89	±1.88	17.654	±0.784	−0.819	0.415
SpO_2 (%)	T0	97.564	±1.54	97.105	±1.0578	−1.737	0.086
	T1	98.654	±0.89	98.2547	±1.21345	−1.876	0.064
	T2	98.65	±1.8	98.24	±0.94651	−1.426	0.157
	T3	97.65	±1.246	97.445	±0.78730.	−0.984	0.328
	T4	98.675	±1.687	98.254	±1.18	−1.446	0.151
	T5	97.857	±1.887	98.077	±0.879	0.747	0.456

Table 4 Intraoperative complications.

	D		M		Total		Chi-square	
	N	%	N	%	N	%	X^2	P-value
Bradycardia	10	20.00	6	12.00	16	16.00	0.670	0.413
Hypotension	15	30.00	5	10.00	20	20.00	5.062	0.024*
N&V	4	8.00	3	6.00	7	7.00	0.00	1.000

Table 5 Postoperative variables.

Postoperative	D (n = 50)	M (n = 50)		
VAS	4.51 ± 1.77	6.54 ± 1.87	5.575	< 0.001*
Postoperative rescue analgesic (If VAS > 4) n(%)	32(64%)	47(94%)	11.814	<0.001*
Time to achieve to 10 in Aldrete score	12.54 ± 2.054	11.879 ± 1.987	−1.636	0.105
Patients satisfaction (5–7)	40(80%)	30(60%)	3.857	0.049*
Doctors satisfaction (5–7)	38(76%)	27(54%)	4.397	0.036*

two agents from the start allows the use of lower dose of each and hence decreasing its own undesired effects and gains the augmented desirable effects of each.

We compared the efficiency and safety of dexmedetomidine/nalbuphine versus midazolam/nalbuphine as intravenously administered agents for MAC during surgical ear procedures conducted under local anesthesia. We found that mean Ramsay Sedation Score (RSS) was significantly more in dexmedetomidine/nalbuphine group (group (*D*)) than in midazolam/nalbuphine group (group (*M*)). Rescue sedation with propofol infusion to achieve target sedation level (Ramsay score of 3) was required by significantly higher number of patients in group (*M*) (50%) as compared to group (*D*) (26%).

The sedative effects of midazolam are mediated through GABA receptor activation. Midazolam could reduce pain perception by reducing the emotional component of pain through its anxiolytic and amnestic effects as anxiety and pain are intimately related so that anxiety leads to an exacerbation of pain [14].

Dexmedetomidine has a high ratio of specificity for the α2 versus the α1 receptor (200: 1 for clonidine and 1600: 1 for dexmedetomidine). Through presynaptic activation of the α2 adrenoceptors, it inhibits the release of norepinephrine and subsequently decreases sympathetic tone. It also attenuates the neuroendocrine and hemodynamic responses to anesthesia and surgery, leading to sedation and analgesia [15]. The highest density of α2 receptors has been detected in the locus ceruleus, the predominant noradrenergic nucleus in the brain and an important modulator of vigilance. The sedative effects of α2 adrenoceptor activation have been attributed to this site in the CNS, and this allows psychomotor function to be preserved while making the patient rest comfortably, so patients are able to return to their baseline level of consciousness when stimulated which is beneficial for MAC [10]. Both Clonidine and dexmedetomidine seem to offer these beneficial properties, but dexmedetomidine has a shorter half-life, which might be more suitable for MAC. There are reports that dexmedetomidine alone does not appear to be suitable for sedation in patients undergoing cataract surgery and midazolam is a better sedative agent. Although those reports stated that there was a slightly better subjective patient satisfaction with dexmedetomidine, it was found effective for sedation with vascular surgeries [14]. Based on this pharmacologic background, our results may be explained on the fact that dexmedetomidine is a more effective sedative and analgesic agent with better preservation of psychomotor function in the give doses by its sympathetic attenuating effect while midazolam has minimal analgesic effect (emotional component) and its sedative effect.

Nalbuphine is a good analgesic for mild to moderate, but not severe, postoperative pain. It is only available for parenteral use. Onset of action is rapid (5–10 min), and duration of action is long (3–6 h) because of a long plasma elimination half-life (5 h). Hepatic metabolism and fecal excretion account are the main methods of elimination. Nalbuphine (0.6 mg/kg) produces no or minimal hemodynamic changes in ASA classes I and II patients [11].

We observed that intraoperative rescue analgesic requirement was significantly less in group (*D*) (34%) than in group (*M*) (60%), ($p < 0.05$). Postoperative VAS score was also significantly less in group (*D*) (64%) than in group (*M*) (94%). The better analgesic effect of α2 agonists has been demonstrated in other studies too [16,17].

Intraoperative bleeding was significantly less in group (*D*) as compared to group (*M*). Controlled intraoperative hypotension effectively decreases surgical blood loss and improves surgical field exposure which is essential for otology surgeries. Dexmedetomidine facilitates controlled hypotension by decreasing the heart rate, systolic, diastolic and mean blood pressure. Dexmedetomidine was found effective in reducing bleeding in ENT surgeries [18]. We also observed that mean heart rate and mean arterial pressure were significantly lower from baseline at various time intervals in group (*D*) than in group (*M*).

Safety is a main concern for any MAC technique. However, a poorly controlled technique may result in deep sedation or general anesthesia with all its attendant risks. Therefore using more than one agent may allow the anesthetist to use fewer doses decreasing the harmful effects of each and allows augmenting the beneficial effects of each drug used.

Limitations of our study were as follows: firstly, inclusion of a broad variety of Ear surgeries for the study. This needed a lot of surgeons to do different types of surgeries. Secondly, some surgeons refused to give patients local anesthesia, so collecting 100 patients in the study was difficult.

In this study we used two agents for performing MAC for ear surgeries; we found that the combination of dexmedetomidine/nalbuphine is superior to midazolam/nalbuphine as regards level of sedation and operative conditions.

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