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ORIGINAL ARTICLE

Comparison of Dexmedetomidine and Alfentanil during Middle Ear Surgery

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Background: We aimed to compare the effects of controlled hypotension with dexmedetomidine or alfentanil on hemodynamic parameters, surgeon satisfaction and bleeding in surgical field under N_2O-free low-flow sevoflurane anesthesia in patients undergoing middle ear surgery.

Materials and Methods: Forty patients, classified as ASA physical status I-II and candidates for middle ear surgery were randomly allocated into two groups by sealed-envelope method. Before induction Group D (n=20) received 0.1 μg/kg/min dexmedetomidine for 10 minutes and Group A (n=20) received 20 μg/kg alfentanil. Group D received 0.7 μg/kg/hour maintenance dose of dexmedetomidine and Group A 1 μg/kg/min alfentanil up until 30 minutes from the end of the surgery. All patients were had an induction with 6 mg/kg thiopental + 0.1mg/kg vecuronium bromide. Following intubation 3% sevoflurane was administered in a mixture of 2.0 L/min O_2 + 2.0 L/min air and this was followed by low-flow anesthesia to deliver 0.5 L/min O_2 + 0.5 L/min air. During the operation, controlled hypotension level was adjusted to have a systolic blood pressure of 80–90 mmHg and mean arterial pressure of 50–65 mmHg. Hemodynamic parameters were recorded with five minutes intervals. The surgeon, blinded to the study drugs, assessed amounts of bleeding in the operative field and surgeon satisfaction.

Results: Achieving the desired hypotension levels happened later in Group D. At the stage of membrane placement, targeted mean arterial pressures were achieved in both groups. Three patients in Group D required short-term nitroglycerine infusion to reach the desired hypotension levels. The amounts of bleeding and surgeon satisfaction were equal in both groups. The return of hypotensive effect of dexmedetomidine was slower once it was stopped. In Group A, postoperative nausea and vomiting were frequently observed and 0.1 mg doses of naloxone were administered to four patients for two times after extubation.

Conclusion: Although additional hypotensive agent required in dexmedetomidine group and desired hypotension levels were happened lately, there was no difference in the amount of bleeding, surgical view and surgeon satisfaction between dexmedetomidine and alfentanil.

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Introduction

In middle ear surgery, a surgical field free of bleeding is necessary and important at the stage of membrane placement. That corresponds to 60 to 100 minutes into the operation; having more bleeding restricts the surgical field the surgeon can view as well as preventing the membrane from being placed to the correct location. Under the microscope, even a minimal bleeding can seem like a major one and it is especially difficult for the anesthesiologist to provide a bleeding free environment. For these reasons, controlled hypotension is frequently used in middle ear surgery not only to decrease the bleeding but also to control the view in the surgical field.[1- 3]

Several pharmacological agents, including inhalational anesthetics, direct-acting vasodilators, β-adrenergic receptor antagonists and calcium channel blockers were used for controlled hypotension.[4,5] Because of the disadvantages related to these agents, the ideal pharmacological agent for controlled hypotension is still to be found. [6]

Dexmedetomidine is an α_2-adrenoceptor agonist and is more specific to α_2 in comparison to clonidin. In clinical studies, its sedative, analgesic and anxiolytic effects have been demonstrated. Until recently, dexmedetomidine was most frequently used for the mechanical ventilation of adults and as a sedative especially after cardiac surgery.[7,8] Redistribution half-

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life and elimination half-life are 6 min and 2 h, respectively, with no dose-dependent effect.[7] When its pharmacological effects were evaluated in terms of lowering the heart rate and mean arterial pressure, it was considered as a good candidate to be used for controlled hypotension. However, limited amount of studies were performed in different surgical procedures to test its use to this end. [9-11] During dexmedetomidine infusion, the advantages are the absence of reflex tachycardia, the suppression of sympathetic nervous system allowing for not having rebound hypertension. [12,13] Although this novel analgesic agent has good hemodynamic control, there is conflicting data concerning its use during middle ear surgery.

Alfentanil is a synthetic opioid with a rapid onset of action and with a short duration of action; it is less lipid-soluble compared to fentanyl. This characteristic contributes to the fact that alfentanil is less soluble in cerebral tissue. [14,15] Its clearance is not as high as that of fentanyl, yet it has a smaller distribution volume. That is why its half-life is also very short. [16, 17] The latter one allows the physician to control its concentration during and following the infusion. [18, 19] It has been usually used as an adjuvant in middle ear or in other surgery [20]. Despite of low cost and postoperative analgesic effect, postoperative respiratory depression and prolonged recovery might be a problem for alfentanil usage. [21]

Concerning that, in this study we aimed to determine and compare the effects of dexmedetomidine and alfentanil on hemodynamics, bleeding in the surgical field and surgeon satisfaction as well as side effects on patients that having middle ear surgery under N_2O-free low-flow sevoflurane anesthesia.

Materials and Methods

After obtaining the approval of the hospital ethics committee and the informed consents of the patients, 40 patients aged between 19-55 years, having ASA physical status I-II, who were to undergo middle ear surgery were included in the study. Patients with type II diabetes, liver and renal failure, advanced pulmonary and cardiovascular system pathologies, anemia, any known history of allergies for the drugs used in the study, bleeding disorders, possibility of a pregnancy or known pregnancy and those using medications against coagulation cascade were excluded from the study.

The patients were evaluated one day prior to surgery during preoperative evaluation and they were not premedicated. Once they entered the operation room, electrocardiography, non-invasive arterial blood pressure, oxygen saturation measurements and bispectral index (BIS) monitorization were performed. From the dorsal side of the hand, venous access was achieved by using a 18 G cannula. Ringer lactate infusion was administered at a rate of 5 ml/kg/hour. Radial artery catheterization for invasive blood pressure measurement was performed from the non-dominant hand of the patient with a 20 G catheter after local anesthesia with 1 ml prilocaine.

Total volume of the study solutions was 50 ml and they contained 4 µg/ml dexmedetomidine or 100 µg/ml alfentanil. An anesthesiologist who was not involved in the data collection process prepared the study solutions. Another anesthesiologist, who was blinded as to treatment group allocation, collected the data during the operations. The study solutions were administered to the patients with an injector type infusion pump (Pilote A2 I 9, Fresenius Vial S.A., France) as explained below. The patients were randomly allocated into two groups by sealed-envelope method. Group D (n=20) received a loading dose of 1 µg/kg dexmedetomidine for 10 minutes before the induction to be followed by a maintenance dose of 0.7 µg/kg/hour up until 30 minutes before the end of surgery. Group A (n=20) received alfentanil at a dose of 20 µg/kg for 10 minutes before induction to be followed by a maintenance dose of 1 µg/kg/min up until 30 minutes before the end of surgery.

All patients had an induction with 6 mg/kg thiopental and received 0.1mg/kg vecuronium bromide for muscular relaxation, they were then intubated with an endotracheal tube. Following intubation, 3% sevoflurane was administered in a mixture of 2.0 L/min O_2 + 2.0 L/min air with high-flow until end-tidal sevoflurane concentrations reached 2.5%. This was followed by low-flow anesthesia to deliver 0.5 L/min O_2 + 0.5 L/min air. During the operation, controlled hypotension levels were adjusted to have a systolic blood pressure of 80–90 mmHg, mean arterial pressure of 50–65 mmHg. When mean arterial pressure was above the desired levels, first sevoflurane concentrations were to be increased, if the desired levels could not still be reached and then nitroglycerine infusion was to be administered at a rate

of 0.5µg/kg/min. If mean arterial pressure was below the desired level, sevoflurane concentrations were to be reduced first, if desired levels could not still be obtained, 10 mg ephedrine was to be administered. If the heart rate was below 50 beats/min, sevoflurane concentration had to be reduced first, if still not corrected, 0.5 mg atropine sulphate was to be administered.

The amount of bleeding during the operation was identified according to Fromm and Boezzart quality scale 22by a same surgeon blinded to the study groups (0 = no bleeding; 1 = slight bleeding, blood evacuation not necessary; 2 = slight bleeding, sometimes blood has to be evacuated; 3 = slight bleeding, sometimes blood has to be evacuated, operative field is visible for some seconds after evacuation; 4 = average bleeding, blood has to be often evacuated, operative field is visible only right after evacuation; 5 = high bleeding, constant blood evacuation is needed, sometimes bleeding exceeds evacuation). Local anesthetics or vasoconstrictor substances were not used on the operative field during surgery. Surgeon satisfaction was questioned as good= 1, moderate = 2 or unsuccessful = 3.

When oxygen saturation was below 94%, FiO_2 was below 30% or $ETCO_2$ was above 40 mmHg, a plan was made to increase the fresh gas flow to 4 L/min and to exclude these patients from the study.

Thirty minutes prior to the end of surgery, all patients received 4 mg ondansetron for the prophylaxis of nausea and vomiting and intramuscular 75 mg diclophenac sodium was used for postoperative pain control.

Sevoflurane was stopped 10 minutes before the end of surgery. 5 minutes to the end of surgery, fresh gas flow was increased to 100% O_2 and 6 L/min and the patients were extubated.

In Group A, if the O_2 saturation of the patient was below 90% in the period after extubation and if recovery criteria could not be achieved, then 0.1 mg naloxone was given under titration.

During the postoperative period complications like nausea-vomiting, itching and urinary retention were recorded.

Heart rate (HR), systolic arterial pressure (SAP) and mean arterial pressure (MAP), oxygen saturations and BIS values were recorded.

Statistical Analysis

Statistical evaluations were performed by using SPSS 13.00 software programme (SPSS Institute, Chicago, III). Results were expressed as standard deviation or median (minimum-maximum). Statistics of age, weight, height, the duration of surgery, hemodynamic parameters among the two groups were performed by using Mann Whitney-U test; sex, ASA physical scores, surgeon satisfaction and the amount of bleeding were performed by using Chi-Square test. Intra-group evaluations of hemodynamic parameters were performed by Paired t test. The level of significance for all tests was set at $p < 0.05$.

Results

The groups did not differ significantly in terms of age, sex distribution, weight, height, ASA physical status scores (Table 1). When two groups were compared for HR; while it was significantly reduced following a loading dose starting at 30 minutes, after the extubation it was found to be higher in Group D. After the extubation, there was elevation in the heart rate in Group D, but it remained lower in Group A (Figure 1).

Table 1. Demographical data, physical health state, type of surgery and duration of surgery in dexmetedomidine (Group D) and alfentanil (Group A) administered patients.

Characteristics	Group D(n=20)	Group A(n=20)	p
Age, years	30,55±9,97	35,80±9,40	0,095
Weight, kg	72,20±11,20	66,50±13,46	0,154
Length, cm	167,35±10,87	165,95±11,16	0,967
Sex, (F/M)	9/11	10/10	0,755
ASA, (I/II)	13/7	11/9	0,333
Type of surgery (tympanomastoidectomy/tympanoplasty)	17/3	13/7	0,273

** represents the statistical difference between Group D and Group A, p< 0,05.*

When compared for SAP, it was significantly lower at 20th minute after stopping the drug and in the period before extubation in Group D (Figure 2). Dexmedetomidine significantly reduced MAP values in comparison to alfentanil especially after receiving the loading dose of the study drug; 10 and 20 minutes after stopping of the infusion, as well as in the period before and after extubation (Figure 3). Three patients in Group D required short-term nitroglycerine infusion to reach the desired hypotension levels. Neither of the groups required the use of atropine sulphate or ephedrine (Table 2).

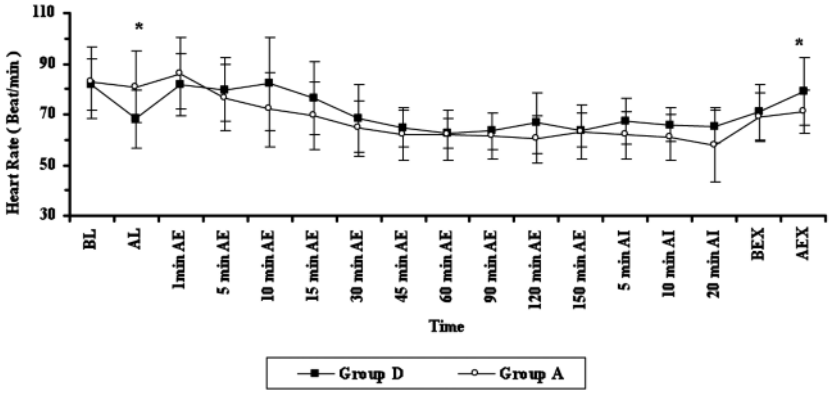

Figure 1. (**BL:** before loading the study drug, **AL:** after loading the study drug, **AE:** after entubation, **IS:** Infüsions were stopped, **BEX:** before extubation, **AEX:** after extubation). Results are means ± SD. * represents the statistical difference between Group D and Group A, p<0,05.

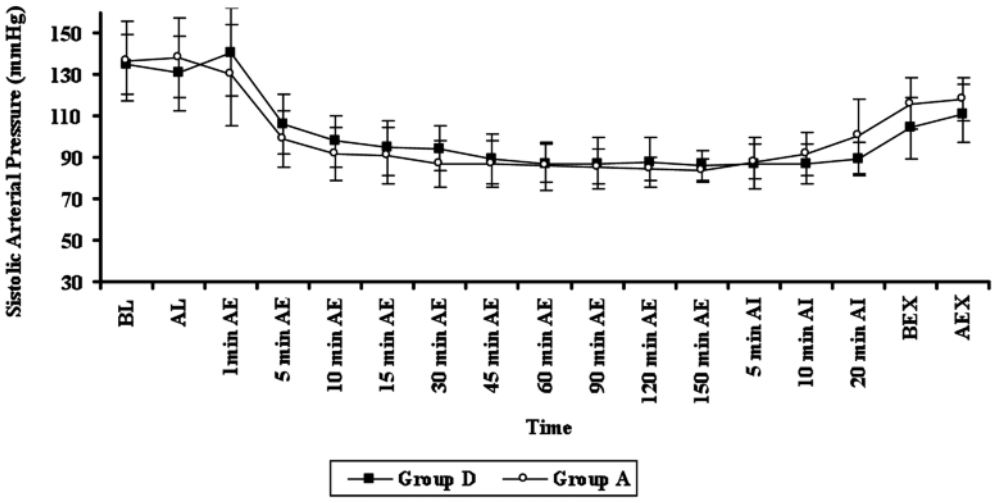

Figure 2. (**BL:** before loading the study drug, **AL:** after loading the study drug, **AE:** after entubation, **IS:** Infüsions were stopped, **BEX:** before extubation, **AEX:** after extubation). Results are means ± SD. * represents the statistical difference between Group D and Group A, p<0,05.

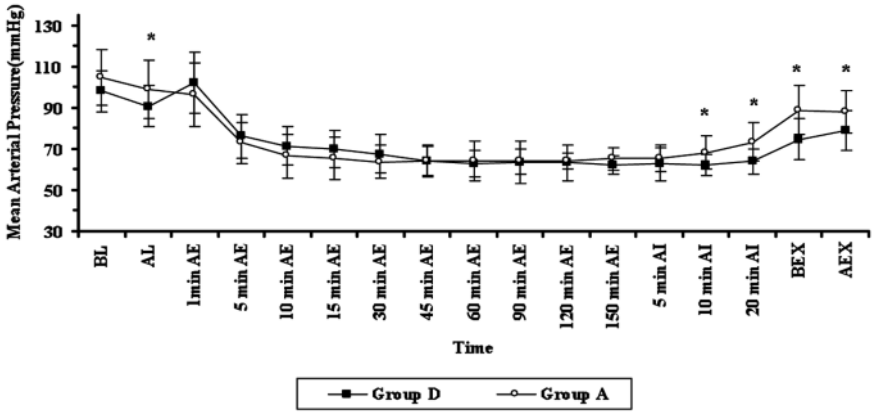

Figure 3. (**BL:** before loading the study drug, AL: after loading the study drug, **AE:** after entubation, IS: Infüsions were stopped, **BEX:** before extubation, **AEX:** after extubation). Results are means ± SD. * represents the statistical difference between Group D and Group A, p<0,05.

Table 2. Bleeding quantity, nitroglycerine and naloxone consumption in study groups

	Group D (n=20)	Group A (n=20)	p
Bleeding quantity in patients (0/1/2/3/4/5) ±			
30 min	14/5/1/0/0	13/6/1/0/0	0,938
45 min		15/4/1/0/0	0,930
60 min	14/5/1/0/0		0,127
90 min		13/6/0/0/0	0,204
120 min	18/2/0/0/0		0,521
150 min		14/2/0/0/0	0,622
	17/0/1/0/0		
		9/3/0/0/0	
	13/3/0/0/0		
		4/1/0/0/0	
	12/1/1/0/0		
Usage of additional drug			
Nitroglycerine (+/-)	3/17	0/20	0,231
Naloxone (+/-)	0/20	4/16	0,106

± According to Fromme and Boezaart et al.'s rating scale

BIS was significantly lower in Group D starting from the end of the loading of the study drug up until 45 minutes and from the moment the infusion was stopped up until before the extubation. Despite this observation, BIS scores remained within the identified range in both groups.

When the two groups were compared for ET Sevo values, there were no significant differences until 45 minutes after the intubation. ET Sevo values significantly elevated in the Group D at 45., 60., 90., 120. and 150.minutes after the intubation, 5., 10, and 20 minutes after stopping of the study drug and before the extubation (Table 3). When the two groups were compared for MAC values; minimum alveolar concentration was statistically higher in the Group D up until 15 minutes after the intubation, at 20 minutes after stopping the study infusions and before the extubation (Table 4).

Table 3. End-tidal sevoflurane values

	Group D (n=20)	Group A (n=20)	p
Before loading	1,83±0,47	1,87±0,37	0,238
After loading	2,51±0,32	2,23±0,40	0,077
1min after entubation	2,78±0,25	2,43±0,37	0,121
5 min after entubation	3,00±0,27	2,59±0,36	0,489
10 min after entubation	3,17±0,29	2,64±0,35	0,478
15 min after entubation	3,21±0,36	2,55±0,38	0,751
30 min after entubation	2,7±0,36	2,3±0,30	0,269
45 min after entubation	2,44±0,34	2,30±0,37	0,054
60 min after entubation	2,40±0,28	2,30±0,35	0,027*
90 min after entubation	2,27±0,30	2,17±0,41	0,032*
120 min after entubation	2,24±0,36	2,18±0,39	0,005*
150 min after entubation	2,16±0,34	2,05±0,37	0,013*
5 min after end of the infusion	2,08±0,32	2,02±0,33	0,011*
10 min after end of the infusion	1,99±0,24	1,73±0,34	0,007*
20 min after the of the infusion	1,77±0,38	1,61±0,33	0,009*
Before extubation	1,43±0,27	1,24±0,28	0,030*
After extubation	0,61±0,12	0,44±0,09	0,0001*

End-tidal sevoflurane values of dexmetedomidine (Group D) and alfentanil (Group A) administered patients. Et sevo values are with mean values ± standard deviations.

** represents the statistical difference between Group D and Group A, p<0,05.*

Table 4. Minimal alveolar concentration values

	Group D (n=20)	Group A (n=20)	p
Before loading	0,95±0,21	0,89±0,13	0,342
After loading	1,56±0,15	1,26±0,16	0,0001*
1min after entubation	1,55±0,19	1,26±0,20	0,0001*
5 min after entubation	1,31±0,16	1,13±0,15	0,001*
10 min after entubation	1,19±0,17	1,11±0,17	0,158
15 min after entubation	1,17±0,14	1,11±0,18	0,297
30 min after entubation	1,11±0,14	1,11±0,20	0,921
45 min after entubation	1,02±0,17	1,05±0,16	0,662
60 min after entubation	1,04±0,17	1,01±0,17	0,666
90 min after entubation	1,00±0,16	1,13±0,28	0,198
120 min after entubation	0,96±0,14	0,95±0,16	0,843
150 min after entubation	0,94±0,16	0,90±0,15	0,447
5 min after end of the infusion	0,81±0,17	0,7±0,14	0,033*
10 min after end of the infusion	0,43±0,10	0,29±0,11	0,00001*

Minimal alveolar concentration values of dexmetedomidine (Group D) and alfentanil (Group A) administered patients. MAC values are with mean values ± standard deviations.

** represents the statistical difference between Group D and Group A, p<0,05.*

During surgery, throughout the time where microscope was in use, neither of the groups experienced a bleeding of more than 2 based on quality scales by Fromm and Boezzart, and there was no difference between the groups. According to Fromm and Boezzart scales, four patients in Group D and two patients in Group A experienced scale 2 bleedings at different time points (Table 2). Surgeon satisfaction was at good levels except 4 patients at moderate level in Group D and 4 patients in Group A. There were no statistical differences between two groups.

In the Group A, 4 patients used 0.1 mg doses of naloxone for two times. Nausea and vomiting during the postoperative period was observed in 1 patient in Group D and in 8 patients in Group A. There was a significant difference between the groups in this regard. Neither of the groups were encountered side effects like urinary retention or itch.

During the use of low-flow anesthesia, none of the patients had an oxygen saturation of lesser than 94% or a FiO_2 of 30% or a $ETCO_2$ value of above 40 mmHg, so there was no need to increase the flow above 4 L/min.

Discussion

In our study, we used dexmedetomidine or alfentanil to achieve a controlled hypotension with N_2O-free low-flow sevoflurane anesthesia. In both groups, the desired hypotension levels were obtained especially during membrane placement with this anesthesia protocols. However, achieving the desired hypotension levels happened later in patients receiving dexmedetomidine and the return of drug effects was slower once it was stopped. Three patients in Group D required short-term nitroglycerine infusion to reach the desired hypotension levels. Postoperative nausea and vomiting was significantly lower in Group D.

The number of publications mentioning the use of dexmedetomidine in middle ear surgery for controlled hypotension purposes is gradually increasing. [11,23-26] Ulger et al. used dexmedetomidine for having controlled hypotension in middle ear surgery. When compared to nitroglycerine, dexmedetomidine allowed for more stable hemodynamics as well as better surgical field view without causing reflex tachycardia or rebound hypertension[23]. In our study we did not also observed reflex tachycardia or rebound hypertension with dexmedetomidine after the infusion was stopped. Ayoglu and colleagues [24], compared the effects of dexmedetomidine to placebo for achieving controlled hypotension in septoplasty and tympanoplasty patients. .Although they could not obtain the desired blood pressure levels, they identified decreases in the blood pressure compared to preoperative values and they have not experienced any reflex tachycardia with dexmedetomidine. Despite

there was a decrease in the bleeding during tympanoplasty procedures, this was not found to be statistically significant and their bleeding score for dexmedetomidine was 1,8 ± 1,1 . They suggested that this finding might be attributed either to the small sample size or to the fact that less bleeding is seen in tympanoplasty than septoplasty operations in general. Concerning that, to achieve a controlled hypotension in our study, we used an additional hypotensive agent, nitroglycerine, together with dexmedetomidine. However, we did not have control group in our study, bleeding scores were not higher than 2 score and surgical satisfaction was at good level except 4 patients in moderate level.

In a similar manner, Durmus et al. [25] compared the effects of dexmedetomidine and placebo and they observed that the bleeding in the surgical field decreased in the dexmedetomidine group. This study covered patients with septoplasty and tympanoplasty; however, the types of operations were not evaluated separately.

There was only one study comparing dexmedetomidine and short-acting opioids. In this study [11] conducted by Richa on limited number of patients, it has been used dexmedetomidine and remifentanil for having controlled hypotension during tympanoplasty. Both agents provided for a persistent and continuous reduction in the heart rate and arterial pressure without raising the need for an additional hypotensive agent. However, they mentioned that dexmedetomidine was less effective in achieving controlled hypotension, reducing bleeding in the surgical field and in surgeon satisfaction. Also, it resulted in lengthening of the extubation time and led to postoperative sedation. Different from our study, they have used a three-point verbal rating scale to determine the condition of the surgical field and the infusion rate were adjusted for blood pressure, the dose of dexmedetomidine was adjusted to 0.4-0.8 μg/kg/hour to have a mean arterial pressure close to 60mmHg. The authors emphasized the effects of dexmedetomidine on middle ear pressure and stated that its potent vasodilator effects can limit the decrease in the blood flow and the bleeding.

There is only a single study in the literature evaluating the effects of dexmedetomidine on middle ear pressure. In this study, dexmedetomidine infusion given 20 minutes prior to anesthesia induction increased tympanometric parameters despite not exceeding the normal limits. [27]

Our results suggest that alfentanil is effective in obtaining controlled hypotension without an additional potent hypotensive agent and provides appropriate surgical conditions by reducing the amount of bleeding. Conversely, high incidence of nause and vomiting during postoperative period and requirement of naloxone was disadvantages for alfentanil. It is well-known that the most common adverse effects of opioids were nausea, vomiting and respiratory depression. [28]. But, for the stabilization of the tympanic graft and the ossicles, postoperative nausea and vomiting should be kept at minimum during tympanoplasty operations. [29]

Use of N_2O during tympanoplasty might result in the detachment of the membrane from its original site of placement by increasing the middle ear pressure. It is recommended to refrain from the use of N_2O during tympanoplasty [30]. As it is uncomfortable to stop N_2O before placing the membrane and additionally study drugs have analgesic effects, we used N_2O-free low flow anesthesia.

In low-flow anesthesia, awakeness can confront us as a problem. For the objective electrophysiological measurement of the hypnotic component of the anesthetic regimen, BIS was developed. BIS might lead to more accurate titration of anesthetic substances, appropriate use of adjuvant substances, shortening of extubation and recovery periods, increases in the quality of the recovery and higher number of awake patients while decreasing the risk of intraoperative awareness [31,32]. In our study, BIS levels were at the hypnotic range despite being somewhat lower in the dexmedetomidine group.

In lengthened anesthesia with low-flow sevoflurane, exposure to compound A can be higher than that during high-flow sevoflurane anesthesia and this compound has been reported to cause hepatic and renal toxicity in rats. In the literature, we did not come across any study employing controlled hypotension and low-flow anesthesia at the same time. The type of anesthesia we employed and the controlled hypotension can pose risks for kidneys. At that point, not measuring renal function may be a limitation of our study.

In our study, additional hypotensive agent, nitroglycerin, was used at short time period in dexmedetomidine group and desired hypotension levels were obtained lately. Postoperative sedation, nausea and vomiting are disadvantages for alfentanil usage. Although our investigation had limited number of patients, we observed no difference in the amount of bleeding, surgical view and surgeon satisfaction between dexmedetomidine and alfentanil under N_2O-free low-flow sevoflurane anesthesia.

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