Comparing remifentanil, magnesium sulfate, and dexmedetomidine for intraoperative hypotension and bleeding and postoperative recovery in endoscopic sinus surgery and tympanomastoidectomy

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Abstract

The study aimed to compare remifentanil, magnesium sulfate, and dexmedetomidine for intraoperative hypotension, bleeding volume, and recovery time in endoscopic sinus surgery and tympanomastoidectomy (TM). A double-blind clinical trial enrolled the patients undergoing endoscopic nasal sinus surgery and TM at Amirkabir Hospital (Arak, Iran), who were randomly assigned into three groups dexmedetomidine (DEX), remifentanil (REM), and magnesium sulfate ($MgSO_4$) to which we intravenously administered 1 μg/kg DEX, an intravenous dose of 1 μg/kg REM, and 40 mg/kg of intravenous $MgSO_4$, respectively. The blood loss, blood pressure (BP), heart rate (HR), oxygen saturation (SaO_2), and recovery time were recorded. Significant differences were found statistically in bleeding rates among all groups ($P = 0.0001$). The least amount of blood loss (very mild bleeding) was observed at 82.85% in the DEX group. BP and HR were lower in this group than those in the other groups. While recovery score was significantly different in the three groups ($P = 0.007$), the recovery time was the highest in the DEX group, while the least in the REM group. Based on the present results, DEX seems to better prevent from bleeding than the others. Moreover, DEX can cause lower BP and HR in subjects with lower propofol administration, but the recovery time is longer. This study was registered by IRCT2017021114056N11 in Iranian Registry Clinical Center.

Key words: blood loss; Endoscopic; sinus; surgery; dexmedetomidine; magnesium sulfate; remifentanil; tympanomastoidectomy

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Introduction

Functional Endoscopic sinus surgery (FESS) has been employed as a surgical intervention to treat chronic sinusitis in patients with no response to drug therapy,[1] during which the surgical vision may be greatly reduced by a small amount of bleeding.[1,2] Thereby, the intraoperative controlled hypotension (CH) can improve the visibility. This can, however, cause serious complications in the postoperative period, including eye socket infections, visual acuity damage, meningeal infections, and other cases which develops by excess intraoperative bleeding.[2-4]

The goal of FESS is to restore drainage and aeration of paranasal sinuses while mucociliary clearance is naturally maintained.[1,4] During FESS under general anesthesia, a controlled hypotension is provided, which means a deliberate reduction in systolic blood pressure (BP) up to 80–90 mmHg, an arterial pressure of up to 50–70 mmHg, or a decrease up to 30% (relative to mean arterial pressure) to keep tissue perfusion. It can provide better surgical condition, reduce the surgery time, improve the postoperative recovery, and reduce the postoperative endoscopic relapse rate.[4-6] Antihypertensive should ideally include attributes, such as ease of administration, rapid onset and termination of effect, the absence of toxic intermediates produced, minor effect on vital organs, and predictable dose-related effects.[7] Since access to the nasal area is limited, mainly through nostril, and numerous techniques cannot be used to control bleeding in other parts of the body in the surgery, then requiring a method to reduce intraoperative bleeding.[8,9] Several methods availably used to control intraoperative bleeding include: local vasoconstrictors, antihypertensives, severe carbon dioxide (CO_2) control, β-blocker pretreatment, reverse trendelenburg, intravenous and inhalation anesthetics, direct vasodilators (such as nitroglycerin and sodium nitroprusside), α-adrenergic agonists (such as clonidine and dexmedetomidine), calcium channel blockers, prostaglandin E1 (alprostadil) and adenosine, hydralazine, trimethaphan and fenoldopam.[1,4] Moreover, anesthetics can reduce bleeding and improve the vision of the surgical field by vasodilation and hypotension, among which magnesium sulfate ($MgSO_4$) has been proven to have positive effects on postoperative bleeding control.[7,8] Magnesium is an N-methyl-D-aspartate (NMDA) receptor antagonist reducing the need for analgesics and sedatives, and competes with calcium in the neural canals, thereby inhibiting the release of acetylcholine (ACh) at the motor end plate.[10] It also acts as a vasodilator by increasing prostacyclin synthesis and by inhibiting the angiotensin-converting enzyme (ACE), while being widely used in patients with preeclampsia and pheochromocytoma.[2,11]

Dexmedetomidine is a highly selective α2-adrenergic receptor agonist, with sedative, amnestic, and analgesic properties.[12] Moreover, the imidazole agent has a decongestant

effect, inducing hypotension during tympanoplasty.[13] An elimination half-life of 2 hours and a distribution half-life of 6 minutes have made it an ideal drug for intravenous infusion. Moreover, this is used in patients undergoing septoplasty under local anesthesia and has been reported to reduce bleeding score.[3,14] It also reduces both intraoperative and postoperative opioid requirement, and has a sympatholytic effect, decreasing the stress response to surgery and ensuring a stable hemodynamic state, while its central and peripheral sympatholytic performance is mediated by alpha-2 receptor, is manifested by reduced arterial BP, HR, cardiac output, and reduced release of norepinephrine.[3,14,15]

With a short-acting μ-opioid agonist, remifentanil has recently been identified as an agent for CH, which is characterized by its fast start and end of an action. When used with propofol or other inhaled anesthetics, it causes CH and improves visualization of the surgical field without affecting the local tissue circulation.[1,6] Remifentanil by infusion leads hypotension and bradycardia. Little information was found about other hemodynamic variables such as changes in cardiac output, stroke volume, and total peripheral resistance (TPR).

No studies have been conducted on the effects of remifentanil, dexmedetomidine and $MgSO_4$ in producing CH and providing favorable intraoperative conditions through different surgeries. But given that previous studies which examine dexmedetomidine and remifentanil, have achieved different, sometimes conflicting results,[3,14-16] the present study aimed to introduce a magnesium sulfate to control intraoperative BP and to obtain recovery discharge criteria, compared with the others. Mainly comparing both in different conditions and surgical procedures, the previous studies did not explore the three anesthetics in a single study; while all were studied in three groups with almost identical conditions under the same procedures in our work.

Subjects and Methods

A double-blind clinical trial involved the patients undergoing endoscopic nasal sinus surgery and TM at Amirkabir Hospital, after obtaining written consent and verifying inclusion and exclusion criteria. The patients and data collection practitioner did not aware about the treatment allocation. Inclusion criteria: age 18–60, American Society of Anesthesiologists (ASA) I-II[17]; Exclusion criteria: age under 18 or above 50, ASA > II, coagulation disorders, history of cardiovascular and cerebrovascular disease, poor BP control, pregnancy, addiction to opioids, body mass index (BMI) > 35, intraoperative systolic BP < 65 mmHg, surgical duration less than 30 minutes and more than 160 minutes, the need for intraoperative sympathomimetic drug, and the use of other hypotensive drugs. The sample size calculated by the Cochrane formula with considering $\alpha = 0.05$ and study power equal 80%. Overall, 130 patients enrolled and after describing the study objectives 105 patients were singed the informed consents and entered in study. The ethical committee of Arak University of Medical Sciences approved this project IR.ARAKMU.REC.1395.359. Moreover, this study was registered by IRCT2017021114056N11 in Iranian Registry Clinical Center.

All patients, admitted one day before surgery, were fasting for 8 hours. After demographic data was recorded, two intravenous lines were inserted in different areas on arrival to the operating room, to inject the three drugs studied and intravenous fluids (or other drugs) into the first and second lines, respectively. Before induction, heart rate (HR), arterial BP and oxygen saturation (SaO_2) were measured. Meanwhile, a left radial arterial line was inserted for an accurate estimate of changes in BP/HR of all subjects, while aggressively and instantaneously measuring the patient's BP from the time of induction.

At the start of induction, 5 mg/kg crystalloid fluid was infused and 100% oxygen was administered to patients through the mask for the first 2 minutes. Anesthesia was induced with 1 μg/kg fentanyl and 5 mg/kg nesdonal, and tracheal intubation was performed with 5.0 mg/kg atracurium. Each patient was mechanically ventilated to maintain an exhaled carbon dioxide concentration of 30–35 mmHg and a SaO_2 of more than 95%. The 105 eligible patients were assigned into three groups by block randomization equally. The Consort chart is depicted in **Figure 1**.

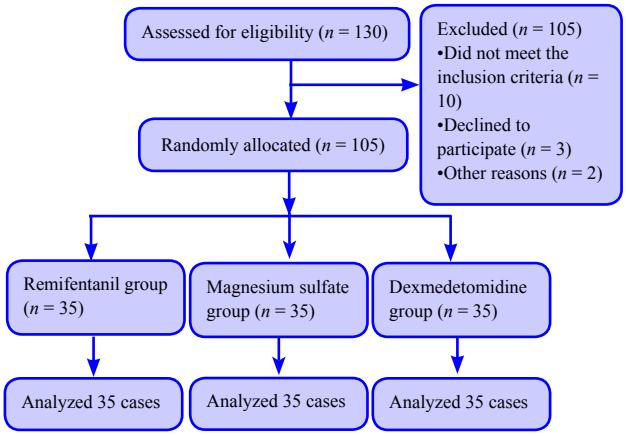

Figure 1: The flowchart of patients.

In the dexmedetomidine group, dexmedetomidine (precede, hospira Co., USA) was administered at 1 mg/kg in 100 mL with normal saline as an initial dose for 10 minutes, followed by 0.4 μg/kg per hour to keep the dose of infusion. In the remifentanil group, remifentanil (Ultiva, GlaxoSmithKline Co., Italy) was intravenously administered at a dose of 1 μg/kg in 100 mL with normal saline for 10 minutes, while the infusion dose was 0.25 μg/kg per minute. With an infusion dose of 10 mg/kg per hour, $MgSO_4$ group was injected with 40 mg/kg of intravenous $MgSO_4$ (Paya Ghasd Darou, Iran) in 100 mL normal saline for 10 minutes before anesthesia induction. Moreover, general anesthesia was maintained with isoflurane (1%) (flurane, Baxter Co., USA).

An intravenous infusion of propofol was commenced at a dose of 50–150 μg/kg per minute in separate IV line after induction to prevent hypertension in all patients and achieve a mean arterial pressure of 65 mm Hg and HR of 75 per minute, while total propofol dose was recorded for each patient. HR, systolic/diastolic BP, and SaO_2 were measured and recorded after induction and during the hypotension phase every 10 minutes until the end of surgery. Before the procedure, the surgeon used 3 mL of intradermal injection of lidocaine (2%) with epinephrine 1:200,000 to produce local vasoconstriction in the area of surgery. Based on the satisfaction scoring system of surgeons (0–6), the surgeon which assessed the surgical site for bleeding and rated it was blind on classifications of the study and had no information on anesthesia drug. The system includes: 0 = no bleeding; 1 = very mild bleeding (can be considered dry); 2 = mild bleeding (does not distort the cut area); 3 = moderate bleeding (affects the area); 4 = severe

Table 1: Comparing the multiple variables among dexmedetomidine, remifentanil and magnesium sulfate groups

Item	Dexmedetomidine	Magnesium sulfate	Remifentanil	*P* value*	Between groups**
Surgery time (minute)	125.26±6.176	126.34±6.197	124.57±3.81	0.402	–
Bleeding score	1.11±0.40	2.06±0.64	1.74±0.70	< 0.001	D with M and R
Extubation time (minute)	143.49±8.36	138.60±7.26	137.60±5.84	0.002	D with M and R
Recovery time (minute)	46.03±5.31	30.83±4.76	28.89±3.65	< 0.001	D with M and R
Recovery score	9.40±0.49	9.77±0.43	9.60±0.49	0.006	D with M
Propofol dose (μg/kg/min)	657.51±061.39	983.0±74.53	802.0±23.98	< 0.001	D with M with R

Note: Data are expressed as the mean ± SD. *Based on analysis of variance; **Based on Tukey *post hoc* test. D: Dexmedetomidine group; M: magnesium sulfate group; R: remifentanil group.

Table 2: Comparison of bleeding severity in dexmedetomidine, remifentanil and magnesium sulfate groups

Bleeding severity	Dexmedetomidine	Magnesium sulfate	Remifentanil	*P* value
No bleeding–very mild	30(85.7)	6(17.1)	14(40)	< 0.001
Mild	5(14.3)	21(60)	16(45.7)	
Moderate	0	8(22.9)	5(14.3)	

Note: Data are expressed as number (percent), and analyzed by chi-square test.

bleeding (can be controlled but destroys it); and 5 = very severe bleeding (cannot be controlled). In the scoring of bleeding, a score of ≤ 2 is favorable for surgical site.

Five minutes before the end of surgery, anesthetic gas was turned off and infusions were stopped. Extubation time was determined based on the good respiration volume and airway reflexes return, and the patient's recovery discharge time was evaluated using Aldrete score, to obtain a score of 9 or higher. This is recorded on the patient's assessment form. Then the patient was transferred to the ward, if scored a 9 or higher. Finally, side effects such as intraoperative hypotension (< 65 mmHg) and bradycardia (HR < 50 beats per minute), and postoperative complications such as nausea and vomiting, muscle stiffness and tremor were recorded. In case of using other antihypertensives, they were recorded on the patient's assessment form, and then the patient was excluded.

Statistical analysis

The data collected were analyzed by Statistical Package for the Social Sciences (SPSS) software version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics such frequency, mean and standard deviation were used for description of patients. Moreover, chi-square test was used to compare the bleeding severity in three groups. Comparing the hemodynamic variables and recovery score and surgery duration was conducted by analysis of variance and Tukey *post hoc* tests. Trend of hemodynamic variables during surgery was assessed by analysis of variance with repeated observations were used in analysis.

Results

The mean age of patients was 33.4 ± 6.27 years that varied between 20 to 52 years and 50.5% of patients were male. Three groups including dexmedetomidine, remifentanil and $MgSO_4$ were same regarding to sex and mean of age and showed that the randomization was appropriate ($P > 0.05$).

The analysis of variance (**Table 1**) showed that there was no significant difference among studied groups regarding to surgery time ($P = 0.402$). But a significant difference was observed among three groups in Bleeding score, extubation time, recovery time, recovery score and Propofol dose ($P < 0.05$). The Tukey *post hoc* test showed that the postoperative recovery time and extubation time were higher in dexmedetomidine group than the other two groups. Moreover, the bleeding score, recovery score and Propofol dose was significantly lower in Dexmedetomidine group than remifentanil and $MgSO_4$ groups.

The chi-square test (**Table 2**) showed a statistically significant difference in bleeding severity among three groups ($P < 0.001$). The least amount of blood loss (no bleeding and very mild bleeding) was observed in the dexmedetomidine group with 85.7%. However, the percent of no bleeding and very mild bleeding in remifentanil and $MgSO_4$ groups were 40% and 17.1%, respectively.

The analysis of variance showed that there was no difference among three groups regarding to BP immediately post induction until 60 minutes after operation ($P > 0.05$). However, a significant difference was observed among groups regarding to BP after the 1st hour to the 150th minute of operation and the BP was significantly lower in dexmedetomidine group than other two groups ($P < 0.001$). In addition, the repeated measurement analysis of varianceshowed that there was a decreasing trend in mean of BP in all three groups after induction and this trend increased 2 hours after induction. However, the mean of BP in the dexmedetomidine group was lower in the remifentanil and $MgSO_4$ groups (**Figure 2**).

As shown in the **Figure 3**, a significant difference was observed in the mean of HR among all groups at all times ($P < 0.01$) from the baseline to the 150th minute after operation. But this difference increased by time. However, the mean of HR was lower than in dexmedetomidine group than remifentanil and $MgSO_4$ groups. Moreover, there was largest difference among groups by increasing time after operation and the HR decrease was more observed in dexmedetomidine group at 1 hour post operation, while the highest HR was observed in the $MgSO_4$ group. The repeated measurement analysis of variance did not show significant decreasing trend in all groups.

The analysis of variance showed that there was no significant difference among three studied groups in SaO_2 at all time after operation ($P > 0.05$), except at 100, 120, 130 and 140 minutes after operation that mean of SaO_2 was lower in

Table 3: Comparison of mean of oxygen saturation (%) in different times after operation in dexmedetomidine, remifentanil and magnesium sulfate groups

Time after operation	Dexmedetomidine	Magnesium sulfate	Remifentanil	*P* value
10 min	96.97±0.822	96.80±0.531	96.60±0.736	0.094
20 min	97.03±0.707	96.94±0.591	96.80±0.584	0.312
30 min	97.03±0.822	97.29±0.957	96.89±0.631	0.12
40 min	96.71±2.177	97.20±0.797	97.34±0.639	0.145
50 min	96.94±0.684	96.86±0.845	97.23±0.547	0.073
60 min	97.29±0.750	97.54±0.741	97.34±0.725	0.315
70 min	97.40±0.775	97.46±0.701	97.31±0.796	0.731
80 min	97.51±0.781	97.57±0.739	97.37±0.690	0.507
90 min	97.71±0.572	97.77±0.646	97.43±0.884	0.103
100 min	97.63±0.547	97.54±0.561	97.89±0.583	0.034
110 min	97.63±0.598	97.49±0.742	97.29±1.582	0.405
120 min	96.74±0.657	96.20±0.797	96.34±0.684	0.006
130 min	96.26±0.741	96.06±0.765	95.77±0.808	0.034
140 min	95.60±0.651	96.06±0.802	95.54±0.886	0.013
150 min	95.66±0.998	95.49±0.702	95.46±0.657	0.53

Note: Data are expressed as the mean ± SD, and analyzed by analysis of variance. min: Minutes.

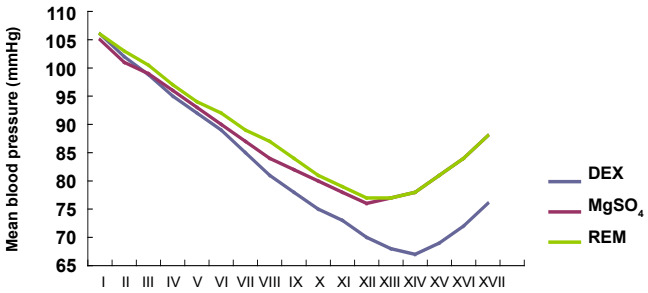

Figure 2: Comparison of mean of blood pressure (mmHg) in different times after operation in dexmedetomidine, remifentanil and magnesium sulfate groups

Note:Data are expressed as mean and analyzed by analysis of variance. I: Baseline (non-invasive); II: immediately post-induction; III–XVII: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150 minutes post operation.

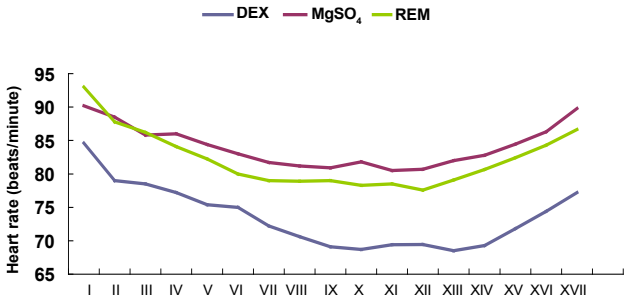

Figure 3: Comparison of mean of heart rate (beats per minute) in different times after operation in dexmedetomidine, remifentanil and magnesium sulfate groups

Note: Data are expressed as mean and analyzed by repeated measurement analysis of variance. I: Baseline (non-invasive); II: immediately post-induction; III–XVII: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150 minutes post operation.

Dexmedetomidine ($P < 0.05$). Moreover, based on repeated measurement test, there was no significant trend in three studied groups (**Table 3**).

Adverse effects

According to our results, no significant difference was found in postoperative complications among the groups ($P = 0.12$). No side effects were observed in the remifentanil group at all, while the most were found in four cases for the dexmedetomidine group, none were seen intraoperatively, and 100% of patients were uncomplicated in the three groups. No significant differences were found statistically in the types of adverse effects in three groups ($P = 0.060$). However, the most adverse effects were observed in Dexmedetomidine group with 4 cases (11.42%) of drowsiness. For $MgSO_4$, there was one case of lethargy and relaxation, and one case of flaccidity. Antihypertensives were not used for the patients in all groups during surgery.

Discussion

According to our results, significant differences were seen statistically in duration of extubation after induction and recovery score and recovery time in the studied groups. The minimum of blood losing, BP and HR was observed in dexmedetomidine and highest recovery score was observed in $MgSO_4$ group. Moreover, no intraoperative side effect was found, and 100% of patients were uncomplicated in all groups. None were observed postoperatively in the remifentanil group, while the most postoperative ones for the dexmedetomidine group with 4 cases (11.42%) of drowsiness. The extubation time and recovery time were longer in the dexmedetomidine group than the others, while the least recovery time for the remifentanil group.

Srivastava et al.[18] study compared the effects of dexmedetomidine and $MgSO_4$ on propofol dose, hemodynamic conditions, and postoperative recovery in patients undergoing spinal surgery, concluding that dexmedetomidine

produced better hemodynamic stability than $MgSO_4$, while the duration of recovery and sedation were the same in both groups, compared to those in the control group. In our study, subjects showed lower BP/HR, less bleeding, and longer recovery time in the dexmedetomidine group, probably due to different doses of $MgSO_4$: 40 mg/kg of intravenous $MgSO_4$ prescribed in our study against 50 mg/kg in their study. By comparing the anesthetic use of dexmedetomidine and remifentanil, another study found that control of bleeding, bleeding rates, and quality of surgeon visibility were not significantly different between both groups, showing a longer recovery time in the dexmedetomidine group than the other group and higher sedation score in the group receiving dexmedetomidine at the first hour postoperative.[19] Their study results are consistent with ours.

A study conducted by Moshiri et al.[15], which compared dexmedetomidine and propofol on hypotension and control of bleeding during ESS, concluded that propofol controls HR better than dexmedetomidine. No significant difference was found in BP of the patients and the quality of the surgical field, as the study's main subject.[19] In our comparative study on dexmedetomidine, remifentanil and $MgSO_4$, dexmedetomidine group had better results, while propofol showed better results in Moshiri et al.'s study,[19] probably due to a difference in anesthetics compared with dexmedetomidine: $MgSO_4$ and remifentanil in our study vs. propofol in theirs. In a study by Kim et al.[20] on the effect of doses of dexmedetomidine and remifentanil on 43 patients in ESS, they found that continuous intraoperative infusion of the first showed the same view of the surgical site (compared with remifentanil) and that time to extubation was also less in the dexmedetomidine group. However, intraoperative hemodynamic changes in the dexmedetomidine group were similar to those in the remifentanil group, having similar hemodynamic stability and recovery discharge criteria in both.[20] However, our study showed that remifentanil achieved a better combination of mild controlled hypotension with less reduction of BP and HR as well as recovery time and dexmedetomidine produced less blood loss, while lower BP and HR. The results of their study are inconsistent with ours.

Another study compared between dexmedetomidine, $MgSO_4$, and nitroglycerin in producing CH during ESS, concluded that the control can be provided by all drugs, but dexmedetomidine was effective. Moreover, the postoperative analgesia and sedation were induced, in the groups of dexmedetomidine and $MgSO_4$. However, the nitroglycerin group achieved a shorter recovery stay and better discharge criteria than the groups of $MgSO_4$ and dexmedetomidine, while subjects in the $MgSO_4$ group also achieved the criteria.[21] The results of their study were in line with our study. Akkaya et al.[22] compared dexmedetomidine and $MgSO_4$ for the quality of visibility in ESS surgery, concluding that dexmedetomidine excursion offers a better visibility of surgical field than $MgSO_4$, and also that dexmedetomidine is a good alternative to $MgSO_4$, since it has a higher reducing effects on bleeding in the surgical field and substantially suppresses HR, as compared with $MgSO_4$. Moreover, they introduced dexmedetomidine as an alternative to $MgSO_4$, due to its shorter duration of surgery.[22] Though our findings are consistent with them, $MgSO_4$, remifentanil, and dexmedetomidine did not vary the duration of surgery in our study.

Comparison of the efficacy of $MgSO_4$ and dexmedetomidine in producing CH in FESS surgeries, showed that the second produced a better hypotension than the other, and provided a higher surgeon satisfaction, and a shorter time to meet recovery discharge criteria for the dexmedetomidine group.[23] The results of their study were consistent in producing hypotension, but the time needed to achieve the criteria was higher in the dexmedetomidine group. Kahveci et al.[24] compared $MgSO_4$ and remifentanil to provide CH in middle ear surgery and concluded that remifentanil produces better CH and surgical conditions for middle ear surgery, as compared with magnesium. The results were consistent with ours.

In another study for comparing dexmedetomidine versus remifentanil for CH during ESS, they concluded that both produce safe and acceptable hypotension, but recovery time of patients in the dexmedetomidine group was longer than the remifentanil group.[25] In our study, dexmedetomidine had a better effect on bleeding control than remifentanil and $MgSO_4$, but with a longer recovery period. The difference could be attributed to different doses: 1 μg/kg dexmedetomidine and 1 μg/kg of intravenous remifentanil in our study *vs.* 0.25 μg/kg/h remifentanil and 0.2 to 0.7 μg/kg/min dexmedetomidine in theirs. Aboushanab et al.[26] compared the efficacy of dexmedetomidine and $MgSO_4$ for CH during middle ear surgery and concluded that both had successful CH, but the subjects in the group of $MgSO_4$ had a lower recovery discharge time and significantly longer recovery time than those in the group of dexmedetomidine,[26] which our results were consistent with theirs. A study by Ryu et al.[27] concluded that both can provide adequate CH and proper conditions in surgical field and that patients receiving $MgSO_4$ had postoperative conditions, postoperative pain and postoperative nausea and vomiting, while remifentanil in our study manifested less blood loss than $MgSO_4$. The difference can be attributed to the difference in the type of surgery performed.

Richa et al.'s study[28] on comparison between dexmedetomidine and remifentanil for CH during tympanoplasty concluded that infusion of 0.4–0.8 μg/kg dexmedetomidine in their study, was less effective in producing CH, creating an appropriate surgical field exposure condition, and lowering the surgeons' satisfaction, as compared with remifentanil, hypotension, while dexmedetomidine was better in our study. The different results can be attributed to different doses of dexmedetomidine: 1 μg/kg in our study *versus* 0.4–0.8 μg/kg in theirs. Eghbal et al.'s study[6] on the comparison of dexmedetomidine and labetalol in controlling bleeding during ESS, showed that a better visibility of the surgical field was seen in the group receiving labetalol than who received dexmedetomidine, and the time required for extubation of patients and the length of time required for recovery was lower in subjects in the labetalol group. Overall, they concluded that labetalol was effective than dexmedetomidine. The results of their study are inconsistent with ours, probably due to the difference in the drugs compared in both studies, but since the patients in the dexmedetomidine group had a longer recovery time than the other group, the Eghbal et al findings are in line with our study.

Regarding the results, the reduced BP/HR, blood losing and the overall amount of propofol administered during surgery in the dexmedetomidine group when compared to the other groups, dexmedetomidine seems to be an effective choice if no high sensitivity was observed to the longer postoperative recovery time. A comparison is recommended between other antihypertensive and anti-nausea and vomiting drugs in other bleeding surgeries, while performing this in other age groups with a larger sample size to introduce and select the safest preferred drug to control intraoperative bleeding.

Author contributions

HM: Contributions to the conception or design of the interpretation of data for the work; and final approval of the article. AM: Contributions to the conception or design of the work and final approval of the article. OR: Contributions the acquisition and analysis of data for the work and drafting the article. AM: Contributions to the conception or design of the work analysis, or interpretation of data for the work; and final approval of the article.

Conflicts of interest

There is no conflict of interest.

Financial support

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Institutional review board statement

The study was approved by the ethical committee of Arak University of Medical Sciences (approved No. IR.ARAKMU.REC.1395.359), and this study was registered by IRCT2017021114056N11 in Iranian Registry Clinical Center.

Declaration of patient consent

The authors certify that they have obtained patient consent forms. In the form, patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Biostatistics statement

The statistical methods of this study were reviewed by the biostatistician of the Arak University of Medical Sciences, Arak, Iran.

Copyright transfer agreement

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Data sharing statement

Datasets analyzed during the current study are available from the corresponding author on reasonable request.

Plagiarism check

Checked twice by iThenticate.

Peer review

Externally peer reviewed.

Open peer review report

Reviewer: Wen-Wu Liu, Secondary Military Medical University, China.

Comments to authors: In this paper, the authors reported two cases of tick bite cellulitis which was successfully treated with ozone. There were some problems in this case report that should be resolved before publication.

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