ORIGINAL RESEARCH

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Effects of dexmedetomidine and esmolol on otoacoustic emissions during controlled hypotensive anesthesia: randomized clinical trial

Abstract

Purpose: The aim of this study was to investigate the ability of esmolol and dexmedetomidine to achieve controlled hypotension on cochlea by measuring otoacoustic emission and stapedius reflex.

Methods: In this prospective, double-blind pilot study, patients scheduled for elective tympanoplasty, rhinoplasty and endoscopic sinus surgery operation were randomly assigned to two groups, and received either dexmedetomidine (n=23) or esmolol (n=24) during surgery to maintain a mean arterial blood pressure between 55 and 65 mmHg. Distortion product otoacoustic emission tests (DPOAE) were performed 24 hours before and after the operation and during surgery (in the 20th and 40th minutes of the operation).

Results: In the intra-group comparison, a statistically significant decrease was present at t₂₀ (2,000 and 4,000 Hz frequency band) and t₄₀ (1,000 and 1,500 Hz) according to the baseline value in the dexmedetomidine group (n=23); in the esmolol group (n=24), a statistically significant decrease (relative to the baseline value) was also detected at t₂₀ and t₄₀ for the 1,000 Hz frequency band. No damage was found on stapes reflexes with the infusion of these drugs.

Conclusions: Infusion of dexmedetomidine and esmolol decreased DPOAE levels during the operations, but DPOAE levels returned to normal in the postoperative period, and had no effect on stapes reflexes. Studies with larger groups of patients are needed to confirm these results in tympanoplasty and other surgeries.

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Introduction

Anesthetic agents may affect cochlear function through their pharmacological features or the hemodynamic changes induced by them; however, there is no known direct neurotoxic effect on the auditory nerve related to any anesthetic agent [1].

There is a cortical organ that perceives hearing on the basilar membrane in the inner ear. There are two groups of sensory cells on the organ of corti: inner and outer hair cells. These cells transform the wave movement of the basilar membrane into the neurochemical signal [2]. Outer hair cells are motile elements, capable of huge amplification of the acoustic wave. Inner hair cells are responsible for coding the audio waves into neural signals and outer hair cells are responsible for fine-tuning the wave activity of the basilar membrane and tectorial membrane [3].

It is estimated that cochlear blood flow in humans is on the order of 1/1,000,000 of the total cardiac output [4]. A decrease in blood pressure may lead to a decrease in cochlear blood flow; in parallel with this, ischemia may occur in the sensory cells. [5]. The preferred measurement method for the determination of damage is otoacoustic emission measurement [2]. Otoacoustic emissions (OAE) are the acoustic energy dispersion that can be determined through the external auditory canal and reveal the condition of the cochlea with high sensitivity and specificity. It is possible to collect information about different sections of the cochlea since emissions are specific to frequency.

Controlled hypotension increases the success of surgical processes by providing a surgical area that is free of blood and by decreasing intraoperative hemorrhage. This method is used for surgeries such as tympanum surgery, endoscopic sinus surgery and rhinoplasty [6]. Vasodilators (nitroprusside, nicardipine and nitroglycerin), α -2_A-adrenergic agonists (clonidine and dexmedetomidine), beta-adrenergic antagonists (propranolol and esmolol), calcium channel blockers and high concentration of inhalation anesthetics are used to provide hypotensive anesthesia [7].

Dexmedetomidine is a highly selective, strong α ₂-adrenoreceptor agonist. It exerts its pharmacologic effect by decreasing heart rate and arterial pressure by means of decreasing plasma norepinephrine and epinephrine [8]. Esmolol is a short-acting β -blocker. Secondary to its negative chronotropic effect, it defuses arterial tension. It provides fine tension stabilization and a surgery area that is free of blood [9].

The aim of the present study was to compare preoperative, peri-operative and postoperative OAE examinations of patients who experienced surgery under

hypotensive anaesthesia, using distortion product otoacoustic emission (DPOAE).

Materials and methods

Study cases

Prior to beginning of this study, an ethics committee approval (protocol #15) was obtained from the Kayseri Training Research Hospital Educational Planning Commission and the Erciyes University Medical Faculty. The working protocol was explained in a way that all patients could clearly understand, and voluntary informed consent was obtained in writing from each patient. Before the first patient was enrolled, the study was registered on ClinicalTrials.gov (identifier number NCT02062333).

Forty seven adult patients between 18 and 50 years of age, ASA I-II group, who had been selected for elective tympanoplasty, rhinoplasty or endoscopic sinus surgery operations, and who planned to implement controlled hypotension during those operations, were included in this study. Surgeries were not done as outpatient procedures and all patients were hospitalized. Those patients who had diseases related to the kidney, liver or cardiovascular system, atrioventricular block, diseases related to the hematologic system, who are morbidly obese (BMI>35), chronic sedative or narcotic users, alcohol or drug addicts, pregnant or those with the possibility of being pregnant, who received anticoagulant treatment, or who had neuromuscular disease were excluded from the study.

Prior to surgery, an otoscopic exam was performed and if findings were normal, it was followed by pure tone audiometry and acoustic emittance measurements. Patients whose 1) pure tone average at 500-1,000-2,000 and 4,000 Hz was over 20 dB, 2) air bone gap was over 5 dB at any frequency between 125-8,000 Hz, 3) tympanometry revealed any type of tympanogram other than Type A or 4) acoustic reflexes were absent at any of the frequencies 500-1,000-2,000 and 4,000 Hz, were excluded from the study.

This study was prospective. Patients were randomly separated into two groups using the coin-toss method: Group Dexmedetomidine (n=23) and Group Esmolol (n=24).

Anesthesia protocol

Premedication was not administered to any patient prior to surgery. Once the patients were taken into the operating room, two venous vascular accesses were established on two different veins in the same arm; one was used for dexmedetomidine (Precedex®, Abbott Laboratory, North Chicago, IL, USA) or esmolol (Brevibloc®; Baxter

Healthcare Corporation, Marion, CA, USA) infusion and the other was for the administration of crystalloid and other medicines. The Allen test was performed for the patients and continuous arterial blood pressure was measured by performing radial artery cannulation with a 22-G arterial cannula for all patients. Cardiac rhythm and rate of patients were followed by performing EKG monitoring with five electrodes (Cardiacap®/5; Datex Ohmeda, Helsinki, Finland). Body temperature was kept between 36°C and 37°C with heat blankets during the surgery [10]. Axillary temperatures were measured by using GE Datex S/5 (System 5) series monitor (GE Datex Ohmeda, Helsinki, Finland). The bispectral index (BIS™; Model- A 2000®; Aspect Medical Systems, Norwood, MA, USA) monitoring was performed to standardize anesthesia depth in both groups. Neuromuscular blockage was measured with a Cardiacap®/5 monitor, which included an NMT module and otomatic train-of-four.

As a standard 2.5 mg/kg intravenous (iv) induction with propofol was administered. To facilitate endotracheal intubation, rocuronium (0.6 mg/kg iv) was administrated to all patients. Anesthesia maintenance was provided with 2% to 4% of sevoflurane. Mechanical ventilation was started by giving a 60% oxygen/air mix to all patients. Mechanical ventilation was administered as a tidal CO₂ concentration of 30–35 mmHg and SpO₂ at >95% level. Subsequent to the intubation process, in order to provide analgesia, remifentanyl was started at an infusion dose of (0.10 microgram/kg/min) to all patients in both groups.

Subsequent to tracheal intubation, esmolol and dexmedetomidine infusions were kept between 55 and 65 mmHg of arterial pressure: for Group Dexmedetomidine patients, maintenance was started with an infusion rate of 0.4–0.8 µg/kg/h after a maximal tolerable dose of 1 µg/kg dexmedetomidine was administered intravenously within 10 minutes [11]. For Group Esmolol patients, the maximal tolerable iv dose of 1 mg/kg of esmolol was achieved within 10 minutes. Following this, continuous infusion was started at a rate of 0.4–0.8 mg/kg/h.

For patient in whom bradycardia (heart rate <50 beats/min) was observed, an atropine bolus of 10 µg/kg was administered intravenously and an ephedrine 6 mg iv bolus was administered if the average arterial blood pressure dropped under 50 mmHg [11]. Remifentanyl infusions were titrated when insufficient anesthesia indications (increment more than targeted mean arterial blood pressure) or somatic responses was observed. All operations were performed by a surgeon who was not aware of the information related to patient care. An anesthetist, who was aware of the treatment groups, was responsible for patient management.

To provide consistency, hemorrhage in the operation area was evaluated by the same surgeons who specialized in a specific surgery type and were blind to the hypotensive agent used. The Surgeons' Scale for Quality of Surgical Field, as described by Fromme et al. [12] was used: 0: no hemorrhage, completely bloodless area; 1: mild hemorrhage, no need for aspiration; 2: mild hemorrhage, rarely requires aspiration, surgical area is clean; 3: mild hemorrhage, requires frequent aspiration, and seconds after hemorrhage, the surgical area is threatened; 4: moderate hemorrhage, requires frequent aspiration, and after aspiration, hemorrhage directly threatens the surgical area; and 5: serious hemorrhage, where hemorrhage is faster than aspiration, the surgical area is severely threatened, and surgery is impossible [12]. A score is ≤2 indicates optimal surgical conditions. No local vasoconstrictor was used for hemorrhage control in any phase of surgery. If the target score was higher than 2 despite the applications of hypotensive study drugs, remifentanyl (as a rescue drug) infusion was increased up to 1 µg/kg/min.

Dexmedetomidine and esmolol, administered by infusion during the surgery, were terminated 5 min earlier than the estimated finish time of surgery. Anesthetic gases were also turned off 5 min before the completion of surgery and patients were ventilated with 100% oxygen at 5 L/min. When the spontaneous breath train-of-four was T1 25%, it was antagonized by administering residual neuromuscular blockage, neostigmine 0.05 mg/kg iv and atropine 0.01 mg/kg iv. The patient was extubated when the train-of-four was T4/T1 90%. The patient was taken to the post-anesthesia care unit after they were completely awake.

The patients were evaluated every 15 minutes with the Aldrete scoring system in post-anesthesia care unit; when this value reached ≥9, the patient was taken to the clinic.

Audiologic evaluation

For each patient, both ears were involved in the study by randomizing those which had equal stapes reflex thresholds; if there was a difference in the stapes reflex threshold between the ears, the ear with the lower contralateral stapes reflex threshold was chosen [13]. Twenty-four hours of preoperative and postoperative stapes reflex were evaluated with an AT 235 interacoustic impedance audiometer (Denmark). The probe tone was 220 Hz. Whether there was stapes reflex on the ipsilateral and contralateral sides, up to a maximum hearing level of 110 Db was assessed by providing increments of 5 dB acoustic signal density. All measurements were performed by an audiologist who was unaware of the patient groups.

The DPOAE was performed on patients using Otodynamics ILO 288 Echoport equipment (Otodynamics, London, UK). All patients with normal otoscopic examination results and stapes reflexes were involved in this part of the study. These measurements were performed pre- (24 hours before) and post-operative (24 hours after) within audio-isolated cabins; rooms where the monitors were muted and ambient voices were decreased to a minimum level in the 20th (t_{20}) and 40th (t_{40}) minutes of operation. Synchronous continuous audio stimulus with pure tones on two different frequencies was given by means of a probe placed in the outer ear for the measurements: $L1=65$ dB (sound pressure level, SP) $L2=55$ dB SPL and $f1/f2=1.22$ were used as stimulus parameters. The DPOAE measurements were performed at seven different frequencies between 1,000 and 8,000 Hz (1,001, 1,501, 2,002, 3,003, 4,004, 6,006 and 7,996 Hz). Again, all measurements were performed by an audiologist who was unaware of the patient groups. By calculating the difference between distortion products and noise, a ± 2 standard deviation signal-to-noise ratio for each frequency was achieved.

Acoustic measurements are difficult to perform in operating rooms because of the high level of ambient noise. Therefore, precautions were taken to avoid the influence of noise as much as possible. Throughout testing, probe stability and noise levels were monitored by the probe microphone and the ILO88 software options. The surgeons and the other staff were instructed to reduce noise as far as possible during the operation. In an attempt to further reduce ambient noise, circumaural ear protectors were fitted to the patient, and the artifact rejection algorithms were adjusted to a maximum between 43 and 48 dB SPL. Under this limit, the mean noise during accepted data was within a reasonable range below 40 dB. The resulting percentage of measurements rejected by the artifact rejection algorithm was equal to or smaller than 50% for all single measurements. Responses were stored after completion of 260 averages for a single measurement.

Statistical analysis

Normal distribution of parametric data was checked using the Shapiro-Wilk test. Comparison of groups was performed with the Student's t-test in groups which demonstrate normal distribution and with the Mann-Whitney U test in groups which did not demonstrate normal distribution. The intra-group comparison of repetitive measurements was performed with One Way Repeated Measures Analysis of Variance. Categorical variables were evaluated with the exact method of the Chi-squared test. All tests were two-sided, and P-values <0.05 were considered significant. All statistical

analyses were performed using the R software packages, version 3.1.1 and MedCalc Software, Version 10.1.6© 1993-2009.

On the basis of the results of the study of Ferber-Viart et al. [1] (DPOAE mean = 8.8 dB, SD = 3.2 dB), the power analysis was based on detecting a difference of 25%. Using a power analysis of 90% and a significance level of 0.05, we predicted the need to include 23 patients in this study.

Results

No statistically significant differences were observed at baseline ($p=0.581$ and $p=0.478$), t_{20} ($p=0.256$ and $p=0.684$), t_{40} ($p=0.534$ and $p=0.962$) or postoperative ($p=0.264$ and $p=0.449$) DPOAE decibel values using the DPOAE intra-group comparison at the dexmedetomidine and esmolol 1,000 and 1,500 Hz frequency bands (Figure 1). In the intra-group comparison, a statistically-significant decrease was seen at t_{40} relative to the baseline value in the dexmedetomidine group at the 1,000 and 1,500 Hz frequency bands; in the esmolol group, a statistically significant decrease relative to the baseline value was also seen at t_{20} and t_{40} for the 1,000 Hz frequency band ($p<0.005$) (Figure 1). No statistical differences were observed at the baseline ($p=0.078$ and $p=0.201$), t_{20} ($p=0.329$ and $p=0.164$), t_{40} ($p=0.509$ and $p=0.904$) or postop ($p=0.326$ and $p=0.686$) DPOAE decibel values using the DPOAE intra-group comparison at dexmedetomidine and esmolol 2,000 and 3,000 Hz frequency bands (Figure 2). In the intra-group comparison, a statistically significant decrease was seen at t_{20} relative to the baseline value in the dexmedetomidine group at 2,000 Hz frequency band ($p=0.005$) (Figure 2).

No statistical differences were observed at the baseline ($p=0.548$, $p=0.832$ and $p=0.182$), t_{20} ($p=0.781$, $p=0.386$ and $p=0.189$), t_{40} ($p=0.991$, $p=0.143$ and $p=0.851$) or postop ($p=0.852$, $p=0.056$ and $p=0.888$) DPOAE decibel values on the DPOAE intra-group comparison at dexmedetomidine and esmolol 4,000, 6,000 and 8,000 Hz frequency band (Figure 3). In the intra-group comparison, a statistically significant decrease was seen at t_{20} relative to the baseline value in the dexmedetomidine group at the 4,000 Hz frequency band ($p=0.031$) (Figure 3). No statistical differences were observed among the average baseline blood pressures ($p=0.170$), during the t_{20} ($p=0.418$) or t_{40} ($p=0.221$) periods (Figure 4). The esmolol group showed a clinically non-critical statistically significant decrease compared with the dexmedetomidine group in the 24th postoperative hour ($p=0.003$) (Figure 4). In addition, no statistical difference was observed between the groups in terms of age, weight, operation duration, sex or average category scale for assessment of the intraoperative surgical field ($p>0.05$)

FIGURE 1. Changes in DPOAE amplitude in the 1,000–1,500 Hz frequency bands

* $p < 0.05$, decreased significantly compared with baseline

Abbreviations: DEX2000, 2,000 Hz DPOAE in Dexmedetomidine Group; DEX3000, 3,000 Hz DPOAE in Dexmedetomidine Group; ESM2000, 2,000 Hz DPOAE in Esmolol Group; ESM3000, 3,000 Hz DPOAE in Esmolol Group; DPOAE, distortion product otoacoustic emission

FIGURE 2. Changes in DPOAE amplitude in the 2,000–3,000 Hz frequency bands

* $p < 0.05$, decreased significantly compared with baseline

Abbreviations: DEX2000, 2,000 Hz DPOAE in Dexmedetomidine Group; DEX3000, 3,000 Hz DPOAE in Dexmedetomidine Group; DPOAE, distortion product otoacoustic emission; ESM2000, 2,000 Hz DPOAE in Esmolol Group; ESM3000, 3,000 Hz DPOAE in Esmolol Group

FIGURE 3. Changes in DPOAE amplitude in the 4,000–6,000 and 8,000 Hz frequency bands

* $p < 0.05$, decreased significantly compared with baseline

Abbreviations: DEX4000, 4,000 Hz DPOAE in Dexmedetomidine Group; DEX6000, 6,000 Hz DPOAE in Dexmedetomidine Group; DEX8000, 8,000 Hz DPOAE in Dexmedetomidine Group; DPOAE, distortion product otoacoustic emission; ESM4000, 4,000 Hz DPOAE in Esmolol Group; ESM6000, 6,000 Hz DPOAE in Esmolol Group; ESM8000, 8,000 Hz DPOAE in Esmolol Group

FIGURE 4. Changes in mean arterial pressures

* $p < 0.05$, significant differences compared with dexmedetomidine group

Abbreviation: DEX, Dexmedetomidine Group; ESM, Esmolol Group; MABP, mean arterial blood pressure

(Table 1). The comparison of intra-group dexmedetomidine and esmolol groups showed no significant differences in the pre-operation and post-operative stapes reflex responses ($p=0.572$ and $p=0.119$, respectively).

TABLE 1. Demographic data of patients

	Dexmedetomidine group (n=23)	Esmolol group (n=24)	p
Age (18–50 years)	29.7 ± 9.0	27.2 ± 11.7	0.415
Weight (kg)	68.8 ± 14.2	69.3 ± 21.2	0.918
Sex M / F (n)	9 / 14	11 / 13	0.770
Duration of operation (min)	97.3 ± 44.9	118.5 ± 51.4	0.141
Surgeons's Scale ^A (0–5)	12 / 11 / 0 / 0 / 0	13 / 11 / 0 / 0 / 0	0.970

^A Surgeons' Scale for Quality of Surgical Field [12].

Discussion

In this study, we used a hypotensive anesthesia method and investigated the effects of various medicines, which are routinely used during surgeries performed under hypotensive anesthesia, on cochlear function. Knowing the ototoxic potential of these medicines, and detecting (early) their potential ototoxicity through the use of dexmedetomidine and esmolol, a patient's hearing can be protected and appropriate medicines for use during the hypotensive anesthesia method can be identified.

Evoked otoacoustic emissions can be reliably measured from nearly all human ears with normal cochlear function, provided that the middle-ear transmissions system is normal. There are two general classes of evoked otoacoustic emissions: transiently-evoked and distortion product otoacoustic. The DPOAE arises from more localized sources of the cochlea and is more frequency sensitive than the transiently-evoked emissions. This is the reason why we preferred to use DPOAE to assess cochlear damage [13].

Premature cochlear damage, which cannot be diagnosed in pure tone audiometry, can be detected with OAE measurements. The OAE measurements can demonstrate cochlear damage objectively [2]; however, other factors that effect OAEs should be considered during the evaluation of results. Those factors include age, sex, body temperature, blood pressure and the outer or middle ear pathologies, which disturb audio transmission. It has been proposed that OAE amplitudes decrease with aging, which is an

independent response to hearing threshold, in comparison studies of different age groups with a normal hearing threshold in pure tone audiometry [14]. Thus, only patients who were younger than 50 years of age and had a normal hearing threshold were included in this study. Older patients were not included because they may not tolerate hypotension because of cerebral perfusion disturbances.

The activity of cochlear efferents of the outer feathery cells was checked through the central neural system. Another method for cochlear efferent activity control is general anesthesia [15]. Liberman et al. reported that increasing anesthesia depth led to a decrease in the olivocochlear efferent system activity [16]. Rhode and Kettner [17] and Evans and Nelson [18] demonstrated the depressive effects of anesthesia on the hearing area of the brain stem. In our study, we provided standardization between these two groups, keeping those BIS score values between 40 and 60 by monitoring anesthesia depth with the bispectral index.

Previous experimental and clinical studies suggest that hypothermia may lead to a decrease in DPOAE amplitude [19]. Borin et al. demonstrated a decrease in amplitude in a study in which DPOAEs was measured during the application of extracorporeal circulation during open cardiac surgery and moderate hypothermia (28°C–29°C). This amplitude decrease was thought to depend on a decrease in DTH activity [20]. A clinical study by Ferber-Viart et al. suggested that hyperthermia (38.4°C) led to a decrease in the TOAE amplitude; and suggested that TOAEs may be affected by body temperature changes [10]. In the present study, preoperative, peri-operative and postoperative body temperatures of patients were recorded and patients kept at a normothermic temperature.

Ogawa et al. demonstrated that dexmedetomidine weakens cerebral blood flow autoregulation and decreases cerebral blood flow [21]. No study has reported on the effects of dexmedetomidine on cochlear blood flow. It may be expected that dexmedetomidine decreases blood flow by breaking cochlear autoregulation, since anesthetic agents have similar effects on cerebral blood flow and cochlear blood flow.

There have been two experimental studies investigating the vulnerability of cochlea to ischemia of the cochlear blood stream using OAE tests [22, 23]. In the present study, cochlear blood stream was stopped for 5 minutes; within seconds, the DPOAE levels decreased and remained low continued during the duration of ischemia.

Mom et al. showed that with the restart of blood flow, DPOAEs returned to original levels [22]. In comparison, Telischi et al. found that DPOAEs did not return to baseline levels, even after restoration of blood flow [23].

Animal studies using laser Doppler flowmetry showed that cochlear microcirculation was similar to the cerebral blood pressure regulation system and sensitive to both systemic arterial pressure and local factors [5]. Otoprotection of the cochlear blood stream, even if less effective than autoregulation of cerebral blood flow, plays a protective role in cases of systemic pressure change on cochlear cells. Other functional studies have shown that there is an association between the brain blood stream and cochlear blood stream. Thus, cochlear blood flow seems to be a way of indirectly showing cerebral blood flow changes [24].

In the present study, DPOAE levels in patients using dexmedetomidine and esmolol showed no statistically significant differences between preoperative and postoperative, or within groups or between groups. Thus, preoperative and postoperative average arterial blood pressure levels were restored in DPOAEs after the hypotensive period, following the surgery.

Viart et al. assessed TOAE levels and found that when propofol and isoflurane were used, both agents caused similar amplitude decreases in the first 20 minutes of the inoperative period; thereafter, amplitude increased in the propofol group but the decrease continued in the isoflurane group. These changes are correlated in blood pressure changes in the propofol group and are independent of blood pressure in the isoflurane group [1]. In our study, in both dexmedetomidine and esmolol groups, the decrease in DPOAE levels was correlated with t_{20} and t_{40} times with hypotensive anesthesia. This correlation suggests that this may be a result of dexmedetomidine and esmolol's effect on the cochlear blood stream. This also shows that these drugs do not exert an effect independent of that on hemodynamics.

Dagal et al., in a compilation paper where they investigated the effects of anesthesia on cerebral autoregulation, showed that cerebral autoregulation can be protected by intravenous anesthesia and that other inhalation anesthetics disrupt the autoregulation of cerebral blood flow, while sevoflurane protects the autoregulation [25]. This is consistent with the present study where we used a combination of propofol and remifentanyl.

Güven et al. found that sevoflurane had systemic hypotensive effects on the cochlear blood stream [13]. In the present study, we evaluated the effects of various anesthesia drugs, as the inhalation anesthetics are far from able to affect the cochlear blood stream. We found that sevoflurane N_2O and propofol may increase the stapes reflex threshold.

In conclusion, we found that DPOAE levels were normal in both dexmedetomidine and esmolol groups during preoperational and post-operational periods. Measurements

in the 20th and 40th minutes of the hypotensive period showed a decrease in DPOAE levels compared with preoperative levels; however, this decrease was not permanent and returned to normal within 24 hours post-operation. This observation shows an association between cochlear blood flow and arterial blood pressure. Thus, we found that hypotension, due to dexmedetomidine and esmolol, caused no permanent damage. There was no effect on stapes reflex during the study period.

References

1. Ferber-Viart C, Preckel MP, Dubreuil C, Banssillon V, Duclaux R. Effect of anesthesia on transient evoked otoacoustic emissions in humans: A comparison between propofol and isoflurane. *Hear Res.* 1998; 121:53-61.
2. Pawlowski KS. Anatomy and physiology of the cochlea in P. S. Roland & J. A. Rutka (eds.), *Ototoxicity 2004*: 1-19. Hamilton, Ontario, Canada: B. C. Decker.
3. Smith CA. Ultrastructure of the organ of Corti. *Adv Sci.* 1968; 24:419-433.
4. Nakashima T, Suzuki T, Morisaki H, Yanagita N. Blood flow in the cochlea, vestibular apparatus and facial nerve. *Acta Otolaryngol.* 1991; 111:738-742.
5. Miller J, Ren TY, Nuttall AL. Studies of inner ear blood flow in animals and human beings. *Otolaryngol Head Neck Surg.* 1995; 112:101-113.
6. Coursin DB, Coursin DB, Maccioli GA. Dexmedetomidine. *Curr Opin Crit Care.* 2001; 7:221-226.
7. Testa LD, Tobias JD. Pharmacologic drugs for controlled hypotension. *J Clin Anesth.* 1995; 7:326-337.
8. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology.* 1992; 77:1134-1142.
9. Degoute CS, Ray MJ, Manchon M, Dubreuil C, Banssillon V. Remifentanyl and controlled hypotension; comparison with nitroprusside or esmolol during tympanoplasty. *Can J Anaesth.* 2001; 48:20-27.
10. Ferber-Viart C, Savourey G, Garcia C, Duclaux R, Bittel J, Collet L. Influence of hyperthermia on cochlear micromechanical properties in humans. *Hear Res.* 1995; 91: 202-207.
11. Richa F, Yazigi A, Sleilaty G, Yazbeck P. Comparison between dexmedetomidine and remifentanyl for controlled hypotension during tympanoplasty. *Eur J Anaesthesiol.* 2008; 25:369-374.
12. Fromme GA, Mackenzie RA, Gould AB Jr, Lund BA, Offord KP. Controlled hypotension for orthognathic surgery. *Anesth Analg.* 1986; 65:683-686.
13. Guven S, Tas A, Adali MK, et al. Influence of anaesthetic agents on transient evoked otoacoustic emissions and stapedius reflex thresholds. *J Laryngol Otol.* 2006; 120:10-15.

14. Keppler H, Dhooge I, Corthals P, et al. The effects of aging on evoked otoacoustic emissions and efferent suppression of transient evoked otoacoustic emissions. *Clin Neurophysiol.* 2010; 121:359-365.
15. Harel N, Kakigi A, Hirakawa H, Mount RJ, Harrison RV. The effects of anesthesia otoacoustic emissions. *Hear Res.* 1997; 110:25-33.
16. Liberman MC. Rapid assessment of sound-evoked olivocochlear feedback: suppression of compound action potentials by contralateral sound. *Hear Res.* 1989; 38:47-56.
17. Rhode WS, Kettner RE. Physiological study of neurons in the dorsal and posteroventral cochlear nucleus of the unanesthetized cat. *J Neurophysiol.* 1987; 57(2):414-442.
18. Evans EF, Nelson PG. The response of single neurones in the cochlear nucleus of the cat as a function of their location and the anesthetic state. *Exp. Brain Res.* 1973; 17(4):402-427.
19. Seifert E, Brand K, van de Flierdt K, Hahn M, Riebandt M, Lamprecht-Dinnesen A. The influence of hypothermia on outer hair cells of the cochlea and its efferents. *Br J Audiol.* 2001; 35:87-98.
20. Borin A, Cruz OL. Braz J Otorhinolaryngol. Study of distortion-product otoacoustic emissions during hypothermia in humans. *Braz J Otorhinolaryngol.* 2008; 74:401-409.
21. Ogawa Y, Iwasaki K, Aoki K, Kojima W, Kato J, Ogawa S. Dexmedetomidine weakens dynamic cerebral autoregulation as assessed by transfer function analysis and the thigh cuff method. *Anesthesiology.* 2008; 109:642-650.
22. Mom T, Avan P, Romand R, Gilain L. Monitoring of functional changes after transient ischemia in gerbil cochlea. *Brain Res.* 1997; 14:751:20-30.
23. Telischi FF, Stagner B, Widick MP, Balkany TJ, Lonsbury-Martin BL. Distortion-product otoacoustic emission monitoring of cochlear blood flow. *Laryngoscope.* 1998; 108:837-842.
24. Kawakami M, Makimoto K, Fukuse S, Takahashi H. Autoregulation of cochlear blood flow. A comparison of cerebral blood flow with muscular blood flow. *Eur Arch Otorhinolaryngol.* 1991; 248:471-474.
25. Dagal A, Lam AM. Cerebral autoregulation and anesthesia. *Curr Opin Anaesthesiol.* 2009; 22:547-552.