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Effects of Esmolol Induced Hypotensive Anaesthesia on Distortion Product Otoacoustic Emission

Esmolol Kullanılarak Oluşturulan Hipotansif Anestezinin Distorsiyon Ürünü Otoakustik Emisyona Etkisi

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ABSTRACT Objective: The aim of this study is to investigate the effects of hypotensive anesthesia induced by esmolol on Distortion Product Otoacoustic Emission (DPOAE) and by this way its availability in cochlear monitoring. **Material and Methods:** This study, includes 25 patients between ages of 18-61 who were operated under general anesthesia. Bispectral Index (BIS) values were maintained in the 40-60 range by infusion of esmolol 50-300 mcg/kg/min, simultaneously with the induction of anesthesia. During surgery, esmolol infusion doses were set to maintain the mean arterial pressure (MAP) approximately 20% below the baseline. Hemodynamic and respiratory parameters and otoacoustic emission measurements were recorded at 0 min. before induction and 3 min., 10 min., and 20 min. after induction. **Results:** No statistically significant differences were observed in terms of DPOAE levels at 1500 Hz, 2000 Hz, 3000 Hz, 4000 Hz, 5000 Hz, and 6000 Hz. No statistically significant correlations were found between the changes of DPOAE levels and percentile changes of hemodynamic parameters according to the Bonferroni adjustment for 3 min., 10 min., and 20 min. time points when compared to zero minute time point. **Conclusion:** In this study, we found that esmolol-induced hypotensive anesthesia has no effect on the DPOAE response. This result is important in showing that the procedure we have been using in lateral skull base surgeries allow secure cochlear monitoring by providing hypotensive anesthesia.

Keywords: Esmolol; anesthesia; otoacoustic emission

ÖZET Amaç: Bu çalışmanın amacı esmolol kullanılarak oluşturulan hipotansif anestezinin DPOAE (distorsiyon ürünü otoakustilk emisyon) yanıtlarına etkisini ve bu yolla koklear monitorizasyonda kullanılabilirliğini araştırmaktır. **Gereç ve Yöntemler:** Bu çalısma, genel anestezi altında opere edilen 18-65 yaş aralığında, 25 hastayı kapsamaktadır. 50-300 mcg/kg/dk esmolol infüzyonu anestezi indüksiyonuyla eşzamanlı uygulanarak, Bispectral Index (BIS) değeri 40-60 aralığında sürdürüldü. Ameliyat süresince, ortalama arter basıncı bazal değerin %20 altında olacak şekilde esmolol infüzyon dozları ayarlandı. Hemodinamik ve solunumsal parametreler ile otoakustik emisyon ölçümleri indüksiyon öncesi 0. dk, induksiyon sonrası 3. dk., 10. dk. ve 20. dk.'da kaydedildi. **Bulgular:** İzlem zamanları arasında 1500 Hz, 2000 Hz, 3000 Hz, 4000 Hz, 5000 hz, 6000 Hz'deki DPOAE düzeyleri yönünden istatistiksel olarak anlamlı farklılık görülmedi. Sıfırıncı dakikaya göre 3., 10., 20. dakikadaki DPOAE düzeylerindeki değişim ile hemodinamik ölçümlerde meydana gelen yüzdesel değişim miktarları arasında Bonferroni düzeltmesine göre istatistiksel olarak anlamlı korelasyon saptanmadı. **Sonuç:** Bu çalışmada esmolol kullanılarak oluşturulan hipotansif anestezinin DPOAE yanıtlarına etkisinin olmadığı saptanmıştır. Bu sonuç kullandığımız prosedürün lateral kafa tabanı cerrahilerinde hipotansif anestezi sağlayarak güvenli koklear monitorizasyona olanak vermesi açısından öneme sahiptir.

Anahtar Kelimeler: Esmolol; anestezi; otoakustik emisyon

Otoacoustic emission test has been widely used in clinical trials since it was introduced by Kempt in 1978 for the first time.[1] It has been preferred in clinical trials due to being simple, cost-effective, non-invasive, and having ability to evaluate frequency specific outer hair cell functions objectively.

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Otoacoustic emission is produced by the vibratory movement of the outer hair cells and transmitted to the external auditory canal and stapedial food plate via basilar membrane and connections outer hair cells.[2] Distortion Product Otoacoustic Emission (DPOAE) is particularly specific in measurement of outer cell functions.[3] It has also been described as the acoustic energy produced in the ear canal by non-linear interaction of primarily applied two simultaneous pure tone frequencies (f1, f2) in cochlea. It is the preferred procedure in diagnosing pathologies involving neurosensory deficits and evaluating cochlear function.[4] DPOAE is a delicate procedure that is affected by many factors including noise, the use of certain drugs, and changes of intracranial pressure and body temperature.[5,6] It may be indicated in conditions such as requirement of anesthesia with hearing monitoring, cerebellopontine angle tumors, such as acoustic neuroma surgery, evaluation of hearing in children and patients with poor cooperation. In such cases the effect of anesthetic agents used, on auditory neurophysiological mechanisms becomes more important. The effects of anesthetics on cochlear functions vary. Anesthetic agents may affect cochlear neurophysiological mechanisms by their pharmacological properties or by affecting hemodynamic parameters. In the literature, human or experimental studies investigating the effects of certain anesthetic agents on acoustic emission responses are available.[7-9]

Hypotensive anesthesia is often preferred for surgery under optimal conditions, for reasons such as improving surgical vision by allowing minimal hemorrhage, decreasing the resulting microtrauma in the tissues by decreasing manipulation, and shortening the duration of the procedure. Especially in cases such as cerebellopontine angle tumors that require precise manipulation, cochlear monitoring and minimal hemorrhage, hypotensive anesthesia is indicated.

In this study we aimed to investigate the effects of hypotensive anesthesia induced by esmolol on DPOAE responses and by this way its availability in cochlear monitoring.

MATERIAL AND METHODS

This prospective, observational study was conducted after obtaining the approval of the Ethics Committee (No. 26379996/160, 10.15.2014) and written informed consent of the patients included in the study. A total of 25 American Society of Anesthesiologists (ASA) I-II patients who underwent surgery under general anesthesia, in the age range of 18-61 years were included in the study. A detailed history was taken from all patients and audiological and otological evaluations were performed. Patients whose examined ear was microscopically, otoscopically and tympanometrically normal were included in the study.

Exclusion criteria included neurosensorial hearing loss more than 30 dB, using ototoxic agents, noise exposure, Menier's disease, chronic otitis media, previous otologic surgery, and metabolic and autoimmune diseases, otologically and severe anemia, atherosclerotic vascular disease (severe CAD, carotid artery stenosis, etc.), cardiac block, uncontrolled hypotension, aortic stenosis, cardiomyopathy, renal and/or hepatic failure, cerebrovascular diseases, and psychiatric diseases, systemically.

This prospective, observational study was conducted at Ministry of Health Ankara Atatürk Training and Research Hospital after obtaining the approval of the Ethics Committee (No. 26379996/160, 10.15.2014) and written informed consent of the patients included in the study.

ANESTHETIC EVALUATION

Demographic data (age, gender, height, weight) of the patients were recorded preoperatively. Then the patients were taken to the operating table; heart rate (HR), systolic-diastolic and mean arterial pressures (SAP, DAP, MAP), peripheral oxygen (O_2) saturation (SpO_2), and body temperature (skin probe) were monitored. Body temperature was maintained in the physiological range. In addition, in order to monitor the Bispectral Index (BIS) value, the BIS sensor was placed appropriately and BIS monitoring was provided by using standard monitors (Datex Ohmeda, SN 6422913, Helsinki, Finland). BIS is the EEG parameter used in the monitorization of sedative and hypnotic effects of anesthetic agents and which helps us to determine the necessary dose of the sedative. After establishing vascular access with a 20 G branule, intravenous (IV) 0.9% sodium chloride infusion

was started at a rate of 2-5 mL/kg/h. Anesthesia was induced by administration of 5 mg/kg thiopental and 1 mcg/kg fentanyl and followed by 0.6 mg/kg IV dose of rocuronium for muscle relaxation. Patients were intubated with appropriate sized tubes at one time. Infusion of esmolol 50-300 mcg/kg/min was co-administered with anesthetic induction. Patients were ventilated with a tidal volume of 6-8 ml/ kg and frequency of 8-12/min by using Drager anesthesia device (Lubeck, Germany). Anesthesia was maintained with 40% O_2 and 60% air and 1 MAC sevoflurane. While end-tidal CO_2 levels were maintained at 32-45 mmHg and BIS levels in 40-60 range, body temperature was maintained in the physiological range. Esmolol infusion dose was set to maintain MAP about 20% below the basal, during surgery.

Hemodynamic and respiratory parameters (SAP, DAP, MAP, HBR, SpO_2) and measurements of otoacoustic emission were recorded at 0^{th} minute before induction and 3^{rd}, 10^{th}, and 20^{th} minutes after induction. When HR decreased below 45 bpm, 0.5 mg of atropine was administered, when MAP decreased below 50 mmHg, 250 ml bolus of IV fluid was given, and if no response is received, 10 mg of ephedrine was administered and esmolol infusion dose was reduced. The patients developing severe recurrent bradycardia attacks (HR <45 min) were administered atropine 0.5 mg IV and excluded from the study. Patients were extubated according to clinical extubation criteria and reversed at the end of the surgery.

OTOLOGICAL EVALUATION AND DPOAE PROCEDURE

All measurements were applied to the right ear. The tests were applied to the normal right ear in patients who have been operated for chronic otitis media. The first measurement was performed prior to the operation in the surgery room. Other measurements were performed by using the same stimulus parameters without removing the probe from the external ear.The second measurement was performed 3 minutes after induction and subsequent measurements were repeated at 10 minute intervals.

Measurements of DPOAE (Maico Diagnostic GmbH, Berlin, Germany) were performed in MB Data mode. Complete silence was ensured during otoacoustic emission measurements in the operating room, including monitors. The ears of the patients were closed with appropriate type of ear probe. Two different speakers and a sensitive microphone were used for frequencies of f1 and f2. The ratio between the frequencies of f2 and f1 (f2/f1) is set as 1.22. Stimulus intensity set as L1 for f1 frequency was and L2 for f2 frequency and L1-L2 was maintained at a level of 10 dB SPL (L1=65, L2=55). The was performed in DP 2f1-f2 custom mode. The results were presented at 1,500, 2,000, 3,000, 4,000, and 6000 Hz frequencies. In the evaluation of the DPOAE results, a "signal-to-noise ratio (SNR)" above 7 dB was considered significant.

STATISTICAL EVALUATION

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). Whether the continuous variables were normally distributed was tested by using Shapiro Wilk test. Data were presented as mean±SD (standard deviation) or number of cases and percentages, where applicable. The differences among repeated hemodynamic measurements were analyzed by repeated measurements of ANOVA, while Friedman test was applied for comparisons of DPOAE levels. Bonferroni adjusted multiple comparison test was used in order to evaluate the significance level when the p-value from the repeated measurements of ANOVA are statistically significant. The associations between continuous variables were evaluated by Spearman's rank correlation analyses. A p value of <0.05 was considered statistically significant. The Bonferroni correction was applied for controlling type I error.

RESULTS

The mean age of the 25 patients included in the study was 31.9±11.0. The operative time ranged between 20 and 29 minutes. The demographic data of the patients were shown in Table 1. No statistically significant differences were found between the time points of measurements in terms of DPOAE levels at 1500 Hz, 2000 Hz, 3000 Hz, 4000 Hz, 5000 Hz, and 6000 Hz (Table 2).

Statistically significant differences were found between the time points in terms of SAP, DAP, MAP, and HBR levels. The SAP levels at the 20^{th}

TABLE 1: The demographic data of the patients.

Variables	n=25
Age (year)	31.9±11.0
Age range (year)	21-61
Sex	
Male	14 (56.0%)
Female	11 (44.0%)
Height (cm)	170.4±7.9
Body weight (kg)	72.1±10.1
Smoking	9 (36.0%)
Accompanying diseases	1 (4.0%)
Drug history	1 (4.0%)
Operation	
Direct Laryngoscopy+Biopsy	1 (4.0%)
Endoscopic Sinus Surgery	2 (8.0%)
Septoplasty	15 (60.0%)
Myringoplasty	7 (28.0%)

minute measurement were significantly lower in comparison with the measurements at the 0th, 3rd, and 10th minutes (p<0.001, p<0.001 and p=0.009, respectively). The DAP levels at the 20th minute measurement were significantly lower in comparison with the measurements at the 0th, 3rd, and 10th minutes (p<0.001, p<0.001 and p=0.003, respectively). In addition, the DAP level at 10th minute was statistically significantly lower than that of at 0th minute (p=0.019). The MAP levels at the 20th minute measurement were significantly lower in comparison with the measurements at the 0th, 3rd, and 10th minutes (p<0.001, p=0.003 and p=0.002, respectively). Statistically significant differences were found in terms of HR levels at 10th and 20th minutes in comparison with 0th minute (p<0.001 and p<0.001) (Table 3).

No statistically significant differences were found in terms of O_2 saturation levels between the time points (p=0.256).

No statistically significant correlations were found between the changes of DPOAE levels and percentile changes of hemodynamic parameters according to the Bonferroni adjustment for the 3rd and 10th minute time point compared to zero minute time point (p<0.0014) (Table 4).

We found no statistically significant correlations between the changes of DPOAE levels and percentile changes of hemodynamic parameters according to the

TABLE 2: DPOAE according to time monitoring of patients.

	0th min	3rd min	10th min	20th min	p value†
1500 Hz	7.6±6.6	8.0±6.6	7.6±8.7	9.1±7.7	0.516
2000 Hz	10.4±7.3	11.8±7.9	11.2±8.8	12.6±9.9	0.863
3000 Hz	12.7±9.9	14.9±8.4	15.3±10.2	14.6±9.3	0.315
4000 Hz	13.3±8.0	13.9±7.8	11.1±8.5	12.1±9.1	0.353
5000 Hz	13.0±9.9	11.7±10.3	12.7±8.7	13.8±9.7	0.879
6000 Hz	12.3±9.4	9.9±10.3	11.2±9.7	13.5±9.7	0.241

†Friedman test.

DPOAE: Distortion product otoacoustic emission.

TABLE 3: Hemodynamic measurements of the patients according to the follow-up time.

	0th min	3rd min	10th min	20th min	p value†
SAP	133.3±17.6^{a}	124.7±18.6^{b}	115.3±28.7^{c}	104.0±18.9^{a,b,c}	<0.001
DAP	84.0±9.0^{a,d}	80.2±14.2^{b}	72.2±17.6^{c,d}	62.2±12.3^{a,b,c}	<0.001
MAP	101.0±10.0^{a}	94.6±16.5^{b}	88.9±21.6^{c}	77.1±14.3^{a,b,c}	<0.001
HBR	84.8±13.9^{a,d}	79.8±26.0	70.6±9.3^{d}	67.7±8.5^{a}	<0.001
SpO2	98.3±1.4	98.8±0.6	98.8±0.7	98.8±0.7	0.256

†Repeated measurements of ANOVA, ^{a}: 20. min with a statistically significant difference between 0. min (p<0.001), ^{b}: 20. min with a statistically significant difference between 5. min (p<0.01), ^{c}: 20. min with a statistically significant difference between 10. min (p<0.01), ^{d}: 10. min with a statistically significant difference between 0. min (p<0.05).

TABLE 4: Correlation coefficients and significance levels between the changes of DPOAE levels and percentile changes of hemodynamic parameters for the 10th minute measurements.

	SAP	DAP	MAP	HR
1500 Hz				
Correlation coefficient	0.498	0.235	0.358	0.032
p- value†	0.022	0.305	0.112	0.891
2000 Hz				
Correlation coefficient	-0.121	0.106	-0.085	0.286
p- value†	0.603	0.649	0.715	0.209
3000 Hz				
Correlation coefficient	-0.090	0.089	-0.049	-0.087
p- value†	0.697	0.702	0.832	0.708
4000 Hz				
Correlation coefficient	0.000	0.160	-0.084	-0.158
p- value†	0.999	0.488	0.718	0.493
5000 Hz				
Correlation coefficient	0.168	0.128	-0.069	0.206
p- value†	0.467	0.581	0.766	0.370
6000 Hz				
Correlation coefficient	-0.028	-0.161	0.055	-0.129
p- value†	0.903	0.486	0.814	0.578

†The results were considered statistically significant for p<0.0014 according to Spearman's correlation test, Bonferroni adjustment.

DPOAE: Distortion product otoacoustic emission, SAP: Systolic arterial pressure, DAP: Diastolic arterial pressure, MAP: Mean arterial pressure, HR: Herat rate.

Bonferroni adjustment for the 20th minute time point compared to zero minute time point (p<0.0014). According to the follow-up time of change, DPOAE level up are shown in Figure 1.

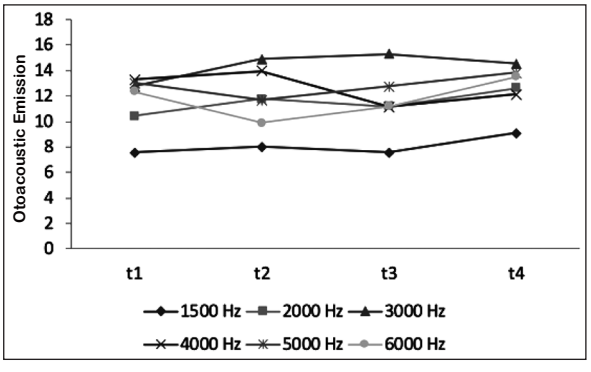

FIGURE 1: According to the follow-up time of change distortion product otoacoustic emission level up.

The center of each point indicates the mean otoacoustic emission levels. There were no statistically significant difference among follow-up times within each Hz levels (p>0.05).

DISCUSSION

The effect of anesthesia on the auditory system is a controversial issue that has been investigated commonly in the studies of auditory neurophysiology. This issue is still unclear because variable findings have been published about the effect of anesthesia on the auditory system. To our knowledge, this is the first study investigating the effects of hypotensive anesthesia induced by beta-1 selective adrenergic blocker, esmolol, on outer hair cell functions. In this study we found that hypotensive anesthesia induced by using esmolol has no effect on DPOAE responses.

Otoacoustic emission test is one of the most important objective tests used in the hearing evaluation. In many cases, it requires to be performed under sdation and general anesthesia. Therefore, evaluating the effects of general anesthetic agents on otoacoustic emission testing is extremely important.

Hypotensive anesthesia is especially preferred in cases requiring precise manipulation such as cere-

bellopontine angle tumor surgery, which also requires auditory monitoring. Controlled hypotension has been used commonly due to advantages such as allowing minimal hemorrhage, improving surgical vision, decreasing the resulting microtrauma in the tissues by decreasing manipulation, and shortening the duration of the procedure.[10] Esmolol is a rapid and short-acting beta-1-selective (cardio-selective) adrenergic blocker, which is effective in controlling perioperative stress responses by decreasing MAP and HR by suppressing sympathetic activity.[11] Pilli et al. in their study compared controlled hypotension and normotensive anesthesia in patients undergoing middle ear surgery and they reported that esmolol is a safe agent that can be used to provide controlled hypotension during the microsurgery.[12] Esmolol controls the systemic blood pressure and heart rate by reducing diastolic arterial pressure less than systolic arterial pressure; this is very important to ensure cerebral perfusion.[13]

Variable findings were obtained in studies investigating the effects of anesthetics on cochlear function. Ferbert-Viart et al. in their study used isoflurane and propofol in order to evaluate transient evoked otoacoustic emission (TEOAE) responses and they found that isoflurane leads to a decrease in TEOAE amplitude due to its own pharmacological properties, whereas propofol leads to a decrease due to hemodynamic changes.[8] However, this reduction was not statistically significant. The small study group including 5 patients in each group was another limiting factor in this study. Conversely, Harel et al. in their animal study with chinchillas by using ketamine and barbiturates, reported that anesthetics increase the DPOAE and TEOAE amplitudes and found that this increase depend on the anesthetic used and emission type. They found that the increase in the amplitude of TEOAE was more pronounced.[14] Boyev et al. in their study conducted on gineapigs, in 2002, found that pentobarbital caused a decrease in the DPOAE response.[9]

Contrary to the studies reporting otoacoustic emission changes, Hauser et al. in their study in which they used methohexital l as an anesthetic agent with midazolam or propofol and fentanyl citrate with a muscle relaxant found that there was no change in TEOAE response.[15] Although they found a minimum decrease in TEOAE amplitude in the nitrous oxide group, that difference was not statistically significant. In the present study, effect was observed when nitrous oxide was included into anethesia protocol. This decrease has been thought to occur due to migration of gas into the middle ear through mucous membrane. Similarly, Hess et al. reported that general anesthesia did not affect otoacoustic emissions response and they suggested that it can be used as a method of objective hearing evaluation in children and patients with poor cooperation.[16] Guven et al. in their study comparing five groups using nitrous oxide, sevoflurane, desflurane, halothane, and propofol + sufentanil did not find any statistically significant changes in TEOAE response.[17] Unlike this study, Ropposch et al. in their study conducted on 30 patients, compared the effects of propofol and sevoflurane on DPOAE response levels, found that both groups were affected.[7] However, this effect was observed at 1.4 kHz while it was not observed over 2 kHz. Since in the present study DPOAE levels over 1.5kHz were compared, absence of effect in high frequencies is compatible with our study. It was thought that this difference was due to the additional use of esmolol in the present study. Again, Drexl et al. found that isoflurane caused an increase in DPOAE amplitude and spontaneous otoacoustic emission incidence.[18]

In the recent studies a 15-20 dB SPL increase has been noted in the ambient noise in the operating room environment, especially at low frequencies, while amount of ambient noise was reported to be minimal at high frequencies.[19] It has been suggested to use high frequencies during intraoperative monitoring for reliability of the responses.[7] Therefore, in this study, we compared the responses at frequencies of 1500 Hz and above.

There are very few studies in the literature investigating the effects of hypotensive anesthetic agents on DPOAE and TEOAE responses.[20,21] In the first study, conducted by Preckel et al., isoflurane and propofol were compared and it has been found that blood flow to the inner ear was autoregulated in the propofol group, whereas no autoregulation was occurred in the isoflurane group. In the second

study, conducted by Aladag et al., propofol and sevoflurane were used in all patients and controlled hypotension was established by using remifentanil and it has been found that DPOAE-SNR levels decreased at each frequencies.[20,21] However, the hypotensive anesthesia protocol used in this study and the time points of audiological tests differ from our study; the first measurement was performed preoperatively and the second measurement was performed on the 15th day postoperatively. In our study, we did not find any statistically significant differences between the time points, in terms of DPOAE levels, at 1500 Hz, 2000 Hz, 3000 Hz, 4000 Hz, 5000 Hz, and 6000 Hz. frequencies (Figure 1). These results are consistent with the studies reporting that anesthetic agents do not affect the cochlear function.[15-17]

In contrast to the studies showing that controlled hypotension affects the DPOAE levels,in this study we found no statistically significant correlation between the changes of DPOAE levels at 3th, 10th, and 20th minute in comparison to 0th minute and the percentile changes in hemodynamic measurements according to Bonferroni correction.

CONCLUSION

In this study, we found that hypotensive anesthesia induced by using esmolol has no effect on DPOAE responses. These results are important with regard to showing that the procedure we use in lateral skull base surgery allows secure cochlear monitoring by providing hypotensive anesthesia. However, larger studies with larger number of patients are needed for a definitive conclusion.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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