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Otoacoustic emission and its application in anesthesia

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Abstract. – **OBJECTIVE: An otoacoustic emission (OAE) is a low-level sound emitted by the cochlea. OAEs are able to objectively evaluate the auditory perception and reflect the functional status of the auditory system. With the characteristics of non-invasiveness, high reliability, and easy manipulation, OAEs have gained wide popularity in clinical audiology and anesthesiology. This review aims to summarize the application of OAE in anesthesia.**

MATERIALS AND METHODS: This study collected data from the databases Web of Science-Clarivate Analytics, PubMed, and Google Scholar in English, covering research in the last 40 years. The keywords were defined as anesthesia, cochlea, OAEs, distortion product otoacoustic emissions, transient evoked otoacoustic emissions, bispectral index, auditory evoked potentials, and depth of anesthesia. Documents that matched defined keywords were selected and reviewed.

RESULTS: Research showed that the types and doses of anesthetic drugs impacted OAEs. Ketamine-based anesthesia has a greater effect on OAE sensitivity over time compared to isoflurane. A higher dose of ketamine-xylazine significantly reduced the amplitude of OAEs. According to those characteristics, OAEs could be used as an objective evaluation method for the effect of anesthetics and have great potential to be applied for anesthetic drug dose control during surgery. OAEs also have been used to detect the cochlear function during anesthesia, which may cause irreversible damage to the cochlea.

CONCLUSIONS: Studies reported that OAEs have been used in anesthesia. However, the existing studies have mainly focused on the influence of anesthetic types or dosages on OAEs. Considering the characteristics of OAEs, such as a convenient measurement, less susceptibility to interference, and fast detection speed, the application of OAE has a great potential in the anesthesia field.

Key Words:
Otoacoustic emission, Distortion product otoacoustic emissions, Anesthesia, Anesthetic depth.

Introduction

An otoacoustic emission (OAE) is a low-level sound emitted by the cochlea spontaneously or in response to an external sound stimulus[1-3]. Kemp firstly recorded the OAE via a combined probe of earphones and microphone in 1987[4,5]. Research has proved that OAE occurs as a byproduct of a unique and vulnerable cochlear mechanism known as the “cochlear amplifier”, contributing significantly to hearing sensitivity and discrimination[6]. In general, OAEs are generated by the motion of the outer hair cells (OHCs) and conducted in a way that is roughly the reverse of sound propagation to the cochlea. This OHCs motion causes the vibration of the basilar membrane, which is conducted by the pressure difference in the cochlear lymph fluid, then pushes the oval window, ossicular chain, and tympanic membrane to vibrate and finally causes the air to vibrate in the outer ear canal[7]. OAEs can be recorded via a probe inserted into the ear canal, as shown in Figure 1. OAEs can reflect the functional status of OHCs. They are sensitive to various hearing impairments and have the characteristics of non-invasiveness, high reliability, and easy manipulation[8]. Therefore, OAEs have been widely applied in clinical treatment and diagnosis, such as hearing screening and examination[9]. Research shows that some anesthetic drugs have ototoxicity, indicating that it is essential to determine if the process of anesthesia significantly alters the

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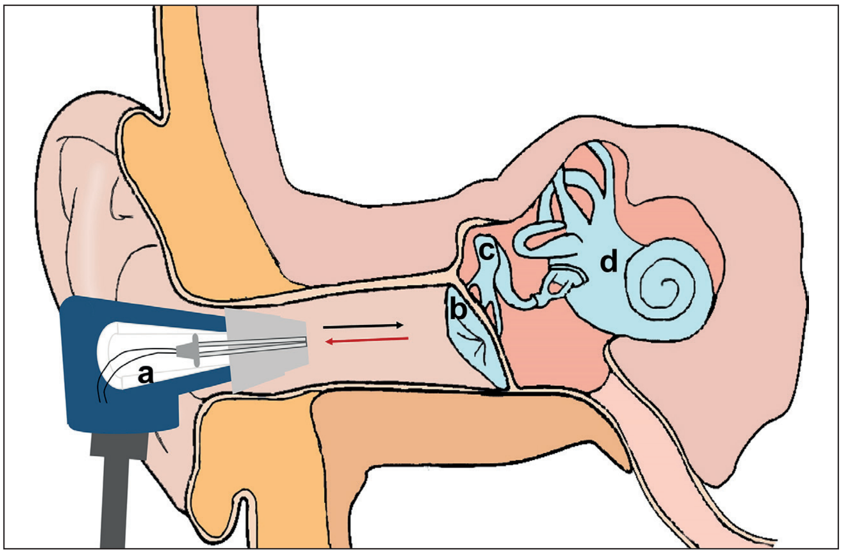

Figure 1. Sketch of OAEs' recording. The probe (**a**) combines an earphone and a microphone. Sound stimuli are emitted into the ear canal by the probe *(black arrow)*. The stimulation is transmitted to the cochlea (**d**) through the vibration of the tympanic membrane (**b**), auditory ossicles (**c**), and oval window. The probe receives the OAEs signal in the ear canal generated from the cochlea *(red arrow)*. OAE: otoacoustic emission.

OAE responses[10]. Moreover, as an objective evaluating tool of auditory perception, OAEs play a vital role in anesthesia because the auditory sense is the last sensation that disappears during anesthesia but the first sensation when awakening[11]. This review summarizes different OAEs and their application in the anesthesiology field.

Materials and Methods

Search Strategy

This study was performed through a literature review on the application of OAEs in clinic and anesthesia. We collected data from the databases Web of Science-Clarivate Analytics, PubMed, and Google Scholar in English, covering research in the last 40 years. The keywords were defined as anesthesia, cochlea, OAEs, distortion product otoacoustic emissions (DPOAEs), transient evoked otoacoustic emissions (TEOAEs), bispectral index (BIS), auditory evoked potentials (AEP), and depth of anesthesia. Documents that matched defined keywords and their combinations were selected.

Articles Screening

Articles screening was conducted by 2 researchers. We screened these articles through two steps. Articles that cannot be read completely were excluded, in the first place. Next, we read the titles and abstracts to further screen out the eligible studies. Finally, we found 78 matching articles.

Results

According to the effective literatures screened, we summarize the characteristics of OAE and its application in clinic. Those studies also reported that OAEs have been used in anesthesia. Interrelated details have been expanded in the following sections.

Otoacoustic Emission

Types of OAE

According to different generation mechanisms, OAEs can be divided into spontaneous otoacoustic emissions (SOAEs) and evoked otoacoustic emissions (EOAEs). The SOAEs are sounds emitted from the cochlea without external stimuli, while EOAEs are evoked by external stimuli. EOAEs can further be divided into TEOAEs, DPOAEs, stimulation frequency otoacoustic emissions (SFOAEs), and electrically evoked otoacoustic emissions (EEOAEs).

The SOAEs recorded in the external ear canal are manifested as single-frequency or multi-frequency narrow-band spectral peaks, and their form is similar to tones[12,13]. The SOAEs can be detected in approximately 50% of the population with normal-hearing via an acoustic probe containing only one sensitive microphone[14,15]. Some studies have shown that contralateral suppression of SOAE can assess efferent auditory system function in individuals with auditory neuropathy spectrum disorder[16].

TEOAEs are the sound frequency energy released in a particular form after an incubation period when the cochlea is stimulated by short-term external impulse sounds (usually within a few milliseconds), and their structure is determined by stimulus characteristics[17]. The most common stimulus in the clinic is an 80 μs sound. In normal-hearing people, the intensity of TEOAEs is about -5 ~ 20 dB SPL (sound pressure level)[18], which can be detected in almost all people younger than 60 years old. Moreover, the detection threshold increases with age at a linear rate of 8 dB/10 years after 40 years old[19].

When an external signal input is applied to a nonlinear system, such as the cochlea, the output may experience two forms of distortion: harmonic distortion and modulation distortion[20,21]. The modulation distortion appears when the input contains more than two frequencies. When the cochlea is stimulated by two pure tones with a certain frequency ratio (called original tones, represented by f_1 and f_2, $f_1<f_2$), there will be frequency distortion products such as $nf_1 \pm mf_2$ (n and m are integers)[22], which is defined as DPOAE. The most prominent product is $2f_1$-f_2, as shown in Figure 2, which is widely used in clinical practice. The sound intensities of original tones are always represented as L_1 and L_2. The lower frequency tone is commonly applied with a higher-level sound stimulation. Therefore, the intensity of L_1 is often no less than L_2. With an easily detected signal and high-frequency specificity, DPOAEs have been widely used to indicate a normal cochlear function in clinical examinations[21].

When the cochlea is stimulated by continuous pure tones, after a certain incubation period, it will emit the same audio frequency energy as the stimulating tones, defined as SFOAE. It is challenging to measure SFOAEs due to the overlap with the evoking stimulus in both time and frequency domains[23]. Similar to other OAEs, SFOAEs can identify the presence of hearing loss. In particular, SFOAEs perform better in predicting auditory status at 0.5 kHz[24]. For the healthy cochlea and even moderate or severe hearing loss, SFOAEs can still be induced in a wide frequency range (0.5 kHz to 8 kHz)[25]. Moreover, SFOAEs show quantitative sensitivity to cochlear injury caused by noise overexposure[26].

EEOAEs are the products of alternating current stimulation acting on the cochlea and have the same frequency as the stimulation current. EEOAEs' temporal structure consists of short and long-delay components, and they have been attributed to the motile responses of the OHCs. The production of EEOAEs benefits from the OHC electromotive response, which is believed to underlie the sharp tuning and exquisite sensitivity of the mammalian cochlea[27].

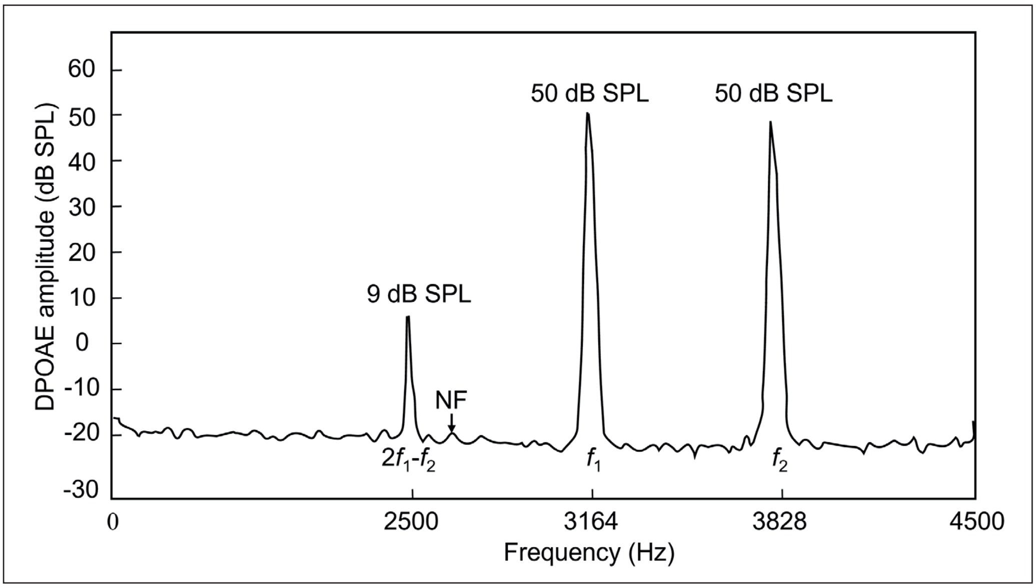

Figure 2. The DPOAE spectrums of normal-hearing people. The frequencies of the two initial pure tones are f_1 = 3164 Hz, f_2 = 3828 Hz. The intensities are L_1=L_2=50 dB. The frequency of DPOAE is $2f_1$-f_2 which is 2500 Hz. DPOAE: distortion product otoacoustic emission, NF: noise floor. Redraw with permission © 1991 Acoustical Society of America.

Applications of OAE

Up to now, OAEs are primarily used to detect ear malfunctions[28], such as hearing impairment, Ménière's disease, and tinnitus[29,30].

Hearing impairment is a common congenital disease with a high incidence rate[31,32]. Universal neonatal screening is the most useful method for the early detection of congenital deafness. DPOAE and TEOAE[33], due to their high signal-to-noise ratio, simple operation, high inspection efficiency, good portability, and noninvasiveness, are suitable tools for newborn hearing screening[4,35].

Ménière's disease is a unique, progressive disease of the inner ear. The underlying etiology of Ménière's disease is not completely clear now, and the complex manifestation poses great challenges for diagnosis[36]. Studies have shown the feasibility of using OAEs to detect Ménière's disease[37]. And TEOAEs' baseline parameters obtained during the onset of Ménière's disease can provide information about the state of OHCs[38]. Therefore, OAEs can be used to explore the pathological mechanism of the hearing symptoms of Ménière's disease and offer a tool for diagnosis[39].

Tinnitus is also a common disease in otology, a subjective symptom formed by the human body under the absence of sound stimulus from the outside[40]. Its incidence is approximately 15% to 20%[41], and it often causes different degrees of hearing impairment in patients. Compared with pure tone audiometry (PTA), OAEs are more sensitive to tinnitus detection[42].

Relationship between Auditory Perception and Anesthesia

Auditory perception is essential for humans to adapt to environmental changes, understand nature, and communicate ideas. It is also the basis of language recognition and understanding. The auditory nervous system has the highest evolutionary degree among the five major human sensory systems. In possession of the most nucleus and complex structure and function, auditory perception is closely related to general anesthesia. Hearing is the last sensation that disappears during anesthesia and the first to be restored when awake[11]. During anesthesia, patients perceive events about the operation and experience intraoperative awareness mainly through hearing.

Intraoperative awareness refers to the unexpected recall of events during surgery by patients who receive general anesthesia, which occurs in 0.1% to 0.2% of general surgeries and 1% of high-risk surgeries[43,44]. Intraoperative awareness will cause a tremendous psychological shadow on the patient, sometimes even resulting in psychological counseling to help the patients alleviate the confusion, stress, or trauma related to this experience. The latest survey by the American Society of Anesthesiologists (ASA) reveals that intraoperative awareness is the second biggest problem that patients are worried about during anesthesia[45,46]. Intraoperative awareness can be divided into 5 levels based on the Michigan awareness classification instrument (MACI), as listed in Table I[47]. Studies showed that most patients who experienced intraoperative awareness could hear doctors' conversations[48,49], and hear the sound first before they feel the pain[50].

Table I. The intraoperative awareness levels classification. "Only hearing" is at the first level and happens in 48%-100% of the patients.

Levels	State
Level 1	Only hearing
Level 2	Tactile perception
Level 3	Pain perception
Level 4	Paralysis perception
Level 5	Paralysis and pain perception

Therefore, auditory research in anesthesia is essential in reducing intraoperative awareness[51-53]. Tools that can directly reflect the auditory system functional status, such as OAEs, may provide an indicator for monitoring intraoperative awareness.

OAEs in Anesthesia

General anesthesia is defined as "an induced state of unconsciousness accompanied by partial or complete loss of protective reflexes" during surgery[54]. Different anesthetics are injected via vein or muscle, or respiratory tract to induce anesthesia and eliminate pain sensation. In recent years, OAEs have been developed for sedation level monitor.

Effect of anesthesia types on OAEs

Different anesthetic drugs have different effects on OAEs[55]. Gungor et al[56,57] induced anesthesia in children with propofol and ketamine and measured OAEs simultaneously. There was a significant difference between the groups at 2 kHz and 3 kHz of post-drug TEOAEs. TEOAEs showed more accurate measurement in the propofol group than in the ketamine group. Therefore, it can be concluded that propofol is a better choice of anesthetic than ketamine to sedate children for OAE measurements. Isoflurane is a volatile inhaled anesthetic and has been widely used in animal research. However, the effect of isoflurane on cochlear function is barely known. Jennie et al[58] used C57Bl/6J and C129/SvEv strains of mice to determine whether isoflurane anesthesia affects hearing function relative to ketamine-based anesthesia using DPOAE. They concluded that OAEs could be used as an objective evaluation method for the effect of anesthetics.

Effects of anesthesia doses on OAEs

Anesthesia doses greatly influence the amplitude of OAEs. Hatzopoulos et al[59] used ketamine-xylazine to anesthetize 72 rats and found that a higher dose of ketamine-xylazine significantly reduced the amplitude of TEOAEs at 2 kHz and 3 kHz. Ropposch et al[60] reported relatively stable DPOAEs when regular drug doses were used to induce anesthesia. Those studies indicate that the amplitudes of OAEs are related to the doses of anesthesia. According to this characteristic, OAEs have great potential to be applied for anesthetic drug dose control during surgery.

Monitoring cochlear function during anesthesia

Studies have proven that anesthetic drugs introduce ototoxicity to impair the cochlear function[61]. OAE is a potential tool to evaluate cochlear function during anesthesia and avoid overdose. Sahin et al[62] determined the effects of intravenous dexmedetomidine on cochlear function during sevoflurane anesthesia by measuring DPOAE and TEOAE in 60 patients under general anesthesia. Results showed a significant decrease in the OAEs amplitude after dexmedetomidine injection, indicating that the micromechanical function of the cochlea was affected. Cubic DPOAEs provide information about the nonlinear gain of the cochlear amplifier. Schlenther et al[63] assessed the influence of ketamine–xylazine anesthesia on the cochlear amplifier by measuring the cubic DPOAEs. They found that the thresholds and the optimum stimulus frequency ratio of cubic DPOAEs changed significantly during anesthesia, which could be the consequence of ketamine-xylazine anesthesia influence on the cochlear amplifier and the cochlear tuning sharpness. Therefore, OAE is a potential tool to monitor the cochlear function during anesthesia, which helps avoid irreversible damage to the cochlea caused by some anesthetics.

Discussion

The existing research on OAEs in anesthesia mainly focus on anesthetics and observe changes in OAE characteristics before and after anesthesia. However, there is still no systematic research on the effect of anesthetic depth on OAEs. The anesthetic depth depends on the balance between the anesthetic dose and the stimulation of surgery, and its monitoring is a vital task during anesthesia[64]. In the past, anesthesiologists judged the depth of anesthesia to adjust the dosage of anesthetics by observing clinical signs, such as blood pressure, heart rate, respiration, sweating, pulse oximetry, tearing, eye movements, facial expressions[65]. However, some drugs, such as muscle relaxants and vasodilators, make it difficult and unreliable to analyze these signs. It becomes impossible to grasp the depth of anesthesia through simple clinical observations fully. Inaccurate assessment of anesthetic depth will cause serious injury to the patient, such as intraoperative awareness, prolonged recovery, mental illness after surgery, and increased risk of postoperative complications[66]. Therefore, it is crucial to strengthen the monitoring of anesthetic depth in patients to reduce the adverse effects caused by underdose or overdose of anesthetics and achieve an ideal state of anesthesia[67,68].

With the development of modern medical technology, objective and quantitative monitoring methods of the depth of anesthesia are gradually applied to the clinic. Electroencephalogram

Table II. Methods of anesthesia depth monitoring widely used in clinics and characteristics.

Features/ Monitoring methods	BIS†	Narcotrend	AEP‡	Entropy
Estimated time delay (awake → deep anesthesia)	~61 s	~26 s	~6 s	~60 s
Susceptibility to interference	Moderate	Moderate	High	High
Appropriate for ketamine or N_2O anesthesia	No	No	No	No

†BIS: bispectral index; ‡AEP: auditory evoked potentials.

(EEG) can reflect the electrical activity of neurons in the cerebral cortex, which is the key to assessing the level of hypnosis[69]. Therefore, most methods of monitoring the depth of anesthesia are based on the different characteristics of EEG[70], such as the BIS, AEPI, and narcotrend index, as shown in Table II. These methods have been used in clinical practice with limitations. For example, the prominent shortcoming of BIS is that its value does not exist independently. In different combinations of drugs, the same BIS value does not mean the same depth of anesthesia[71,72]. Moreover, the time delay from wakefulness to anesthesia in BIS monitoring is severe. The AEPI monitoring is susceptible to interference, such as muscle activity, body movement, and electrocautery. The disadvantage of the narcotrend index is that the anesthesia monitoring index may be inconsistent with the actual state of the patient when the patient has neurological abnormalities and neuro tumors[73-75]. The entropy monitoring also has a significant time delay and high susceptibility to interference. Due to the different action mechanisms of anesthetics, some anesthetics cannot be effectively monitored, such as ketamine and nitrous oxide. With the improvement of technology, an increasing number of characteristic indexes of EEG have been used to monitor the depth of anesthesia. However, no algorithm can identify the turning point of losing consciousness and cannot detect intraoperative awareness.

OAEs have the characteristics of fast speed and convenience. According to the DPOAE testing system made by Tucker-Davis Technologies (TDT, Alachua, FL, USA), DPOAEs can be recorded without sound-attenuating chambers. Therefore, DPOAEs are not as susceptible to interference as an EEG signal. Furthermore, OAEs are easy to collect, which only needs to push the OAE probe into the patient's ear canal. Some studies have shown that the values of DPOAEs will change before and after ketamine inducing anesthesia, although the change mechanism is unclear[58]. Therefore, OAEs may be able to make up for the deficiency of current monitoring methods of anesthesia depth. In future studies, research about the effect of the depth of anesthesia on OAEs can be conducted.

Future Directions

OAE mechanism

Currently, it is believed that the active mechanism of the cochlea produces OAEs, but the detailed mechanism is still not fully understood[76]. Whether the OAEs recorded in the external ear canal are generated by a single or more mechanisms are still unclear. Research has shown that the generation mechanism of OAEs is different between those induced by high-intensity stimuli (> 60 dB SPL) and those induced by low-intensity stimuli, and the latter is more sensitive to various factors that affect cochlear function[77]. Therefore, it is speculated that some non-physiological passive mechanisms could be involved in forming OAEs under high-intensity stimulation. However, some studies believed that OAEs induced by high- and low-intensity original sounds follow the same generation mechanism, but the nonlinear components contained are different in quantity[78]. Further study on the generation mechanism of OAEs is conducive to understanding the effect of anesthetics on OAEs.

OAE calculation speed

At present, the calculation speed of OAEs needs to be further improved. The rate of DPOAE testing using the Signal Processing System III from TDT is 47.7 times per second. The acquisition time for DPOAE with six primary-tone levels for eight audiometric frequencies between 1 and 8 kHz is 100 seconds if the average numbers of signals are 100 times. There is a high requirement for the chronergy of detection technology in clinical anesthesia. Therefore, the acquisition time of OAEs needs to be further improved[77-80]. Shortly, it is expected that, depending on the changed characteristics of OAEs with depth of anesthesia, the acquisition time can be further reduced to somewhere less than 20 seconds by reducing the sound stimuli numbers and the average times [81]. The increase in the calculation speed of OAEs will further expand the application range of OAEs in anesthesia.

OAE application in multiple drugs

Many studies have claimed that different anesthetics have different effects on OAE due to different mechanisms of anesthetics[82]. Most of these studies used a single drug to induce anesthesia, while the combination of multiple drugs is commonly used to induce anesthesia in current clinics. For example, comparing the use of low-dose ropivacaine combined with sufentanil with a single use of ropivacaine during the delivery of pregnant women, the analgesic onset time of the former is significantly shorter than that of the latter. The impact on the newborn is minor, and the analgesic satisfaction of the parturient is higher[83,84]. Therefore, strengthening the research of OAEs in the combined use of drugs is of great significance to clinical anesthesia.

OAE variation during anesthesia

There have been studies on the factors of OAE value changes during anesthesia. For example, when the anesthetic dose was increased, the OAE values changed. The reason may be that the deeper level of anesthesia reduces the supply of blood and oxygen to the inner ear, affecting hair cell activity. Previous studies on pentobarbital[85] and nitrous oxide[86,87] have confirmed that these anesthetics change the middle ear's dynamics, especially the eustachian tube's function. These anesthetics create negative pressure in the middle ear. The relationship between the negative pressure of the middle ear and the level of OAEs has been established[88-90]. For humans and animals, negative middle ear pressure leads to the attenuation of OAE amplitude at a specific frequency. Therefore, when the anesthetic dose is increased, negative pressure may be generated in the middle ear to attenuate the OAE values. Other studies have also shown that changes in cerebrospinal fluid pressure, inner ear blood flow, and hemodynamics affect OAE values. However, the reasons for changes in OAE values in anesthesia have not yet been determined and need further research.

In summary, to further explore OAEs in anesthesia, we need to be clear about the mechanism of OAE generation and then further improve the measurement speed. The mechanism of anesthetics acting on OAEs should also be studied in-depth to investigate the effects of compound anesthesia or anesthesia depth based on OAEs.

Conclusions

Previous studies found that auditory perception is specific in general anesthesia compared to other senses. As a tool for the objective assessment of auditory perception, OAEs have been used in anesthesia. OAEs can monitor the cochlear function during anesthesia and detect the ototoxicity of anesthetics. It can be evidenced that anesthetics affect the amplitude of OAEs. However, existing studies only focused on the influence of the types or doses of anesthetics on OAEs and observed the changes in OAE characteristics before and after anesthesia. Considering the advantages of convenient measurement, less susceptibility to interference, and fast speed with OAEs, the application of OAEs in anesthesia should be further expanded.

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Authors' Contributions

Guangjian Ni, Xiuyun Liu, Yanru Bai, and Wenli Wang contributed to the conception and design of the work, drafting and revising the manuscript. Qi Zheng and Shu Zheng performed the literature search. All authors contributed to the article. All authors agreed to submit the manuscript in its current state and agree to be accountable for all aspects of the work.

Conflicts of interest

The Authors declare that they have no conflict of interests.

Ethics Approval and Consent to Participate

Ethics Approval and Consent to Participate are not required for review articles.

Availability of Data and Materials

All datasets generated or analyzed during this study are included in the manuscript.

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