Assessment of Auditory Function in Patients with Acne Vulgaris receiving Oral Isotretinoin

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Abstract

Background: Isotretinoin is the only available drug that affects all stages of acne pathogenesis and the success of the treatment with oral isotretinoin seems to greatly improve the social functioning of acne patients. Side effects of isotretinoin are well known, but ototoxicity is rarely reported, and its mechanism is not clear.

Objectives: This study was designed to address the possible ototoxic effects of oral Isotretinoin on the inner ears of acne patients.

Patients and Methods: Assessment of the selected sample of patients included full history taking as regards hearing loss, tinnitus, vertigo as well as acne vulgaris. General examination, otorhinolaryngological and dermatological examination were performed. Lipid profile, pure-tone audiometry (PTA) as well as auditory brainstem response (ABR) were conducted both prior to and after oral isotretinoin intake.

Results: There was significant difference between serum blood lipids, ABR latencies as well as PTA thresholds at 3000Hz before and after treatment with oral isotretinoin and highly significant difference between PTA thresholds at 4000,6000 and 8000Hz before and after treatment.

Conclusion: Serum blood lipids seemed to be a good predictor of the adverse effects of oral isotretinoin on human inner ears.

Keywords: Oral Isotretinoin; Pure-tone audiometry; ABR; Lipid profile.

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Background

Isotretinoin, a synthetic retinoid also known as 13-cis retinoid, remains the most effective treatment for severe acne **(Brelsford and Beute, 2008)**. FDA approval for its oral use in such cases dates back to 1982. Additionally, it's utilized for moderate to severe acne cases resistant to standard treatments. Unlike other medications, isotretinoin impacts all stages of acne development, significantly enhancing the social well-being of acne patients **(Charakida et al., 2004)**. Despite its efficacy and generally acceptable tolerance, isotretinoin presents a broad spectrum of side effects affecting mucosa, skin, eyes, liver, bones, and the musculoskeletal system **(Bigby and Stern, 1988)**.

Most common side effects are usually manageable without discontinuing treatment and tend to resolve shortly after cessation **(Karlidag et al., 2002)**. While isotretinoin's side effects are well-documented, ototoxicity is rarely observed, and its underlying mechanism remains unclear **(Thakur et al., 2012)**. Recent reports have highlighted potential adverse effects of hyperlipidemia on auditory function. Boztepe et al. observed a decline in pure tone audiometry thresholds during isotretinoin therapy, correlating with increased triglyceride and total cholesterol levels **(Boztepe et al., 2013; Yaldiz et al., 2020; Tugrul et al. 2019)**.

Hence, this study aims to investigate potential ototoxic effects of oral isotretinoin on the inner ears of acne patients.

Patients and methods

Sixty patients (120 ears) were selected from males and non-pregnant females with moderate to severe acne vulgaris whose age ranged from 15 to 25 years old prior to the administration of oral isotretinoin and 3 months after the regular use of oral isotretinoin as a sole medical treatment using a dosage of 0.5 mg/kg. Exclusion criteria included:

1- Pregnant females or those with contraindications for isotretinoin.
2- Ototoxic drug use, exposure to noise, history of otologic surgery, Meniere's disease, cranial trauma, metabolic disease, autoimmune disease.
3- Patients with liver disease.
4- Patients with hyperlipidemia.

The study design was approved by the research ethics committee at Qena faculty of Medicine (Code: SVU-MED-AUD030-2/690). Each patient signed an informed consent prior to participation in the study. Assessment of the selected sample of patients included full history taking as regards hearing loss, tinnitus, vertigo as well as acne vulgaris. General examination, otorhinolaryngological and dermatological examination were performed. Lipid profile, pure-tone audiometry (PTA) as well as auditory brainstem response (ABR) were conducted both prior to and after oral isotretinoin intake.

Statistical analysis

Statistical analysis using SPSS 16 was conducted. Descriptive statistics, paired T-test, correlation and regression analysis were applied. Level of significance was considered when $p< 0.05$.

Results

Thirty one males and 29 females were included in the study (**Table.1**). (**Tables. 2 & 3**) showed significant difference between PTA thresholds at 3000Hz before and after treatment with oral isotretinoin and highly significant difference between PTA thresholds at 4000,6000 and 8000Hz before and after treatment**.**

Table 1. Demographic data of the study.

Gender	Value (N = 60)
Male	31 (51.67%)
Female	29 (48.33%)
Age (Years)	19.25 ± 2.57

Table 2. Puretone audiometry (PTA) thresholds right ear

frequency	Pre X̄±SD	Post x̄±SD	T	Significance
250	9.49±3.849	11.01±6.277	1.355	0.25
500	10±5.286	10.80±6.452	1.525	0.132
1000	9.35±3.526	10.14±5.214	1.525	0.132
2000	10.43±4.981	10.51±5.761	.113	0.910
3000	10.80±5.046	12.17±6.992	2.362	0.021
4000	8.91±3.193	12.32±5.789	4.839	0.000
6000	10.22±1.999	11.38±6.117	3.710	0.000
8000	11.74±2.399	12.75±5.723	3.506	0.000

Table 3. Puretone audiometry (PTA) thresholds left ear

Frequency	Pre X̄ ±SD	Post x̄ ±SD	T	Significance
250	9.49±3.849	11.01±6.277	1.355	0.31
500	9.78±5.285	10.5±6.455	1.622	0.131
1000	9.52±3.518	10.22±5.208	1.525	0.132
2000	10.43±4.981	10.51±5.761	.113	0.910
3000	10.50±5.044	12.06±6.988	2.235	0.022
4000	8.75±3.089	12.54±5.764	4.833	0.000
6000	10.21±1.995	11.36±6.113	4.711	0.000
8000	11.54±2.399	12.90±5.733	3,821	0.000

(**Tables. 4 & 5**) revealed a highly significant difference between ABR latencies of waves I ,III ,V before and after treatment with oral isotretinoin in both right & left ears. Significant increases were observed in cholesterol (134.38 ± 11.25 mg/dL to 232.93 ± 21.11 mg/dL, $p < 0.0001$), triglycerides (113.57 ± 13.3 mg/dL to 221.88 ± 97.37 mg/dL, $p < 0.0001$), and LDL (80.95 ± 8.45 mg/dL to 125.47 ± 32.25 mg/dL, $p < 0.0001$) post management. Conversely, a significant decrease was noted in HDL (71.57 ± 6.61 mg/dL to 51.33 ± 14.88 mg/dL, $p < 0.0001$) post management compared to pre-management.

Table 4.Auditory Brainstem Response (ABR) latencies right ear

Wave	Pre X̄ ±SD	Post x̄ ±SD	T	Significance
I	1.626±,16686	1.699±.2410	3.092	.001
III	3.726±.1779	3.820±.2530	4.982	.000
V	5.739±.1564	5.836±0.2408	4.963	.000

Table 5. Auditory Brainstem Response (ABR) latencies left ear

Wave	Pre $\bar{X}$ ±SD	Post $\bar{x}$ ±SD	T	Significance
I	1.621±.1665	1.699±.2412	3.087	.002
III	3.833±.1760	3.910±.2530	4.978	.000
V	5.649±.1610	5.852±0.2402	4.961	.000

There was a high correlation between post treatment increases in PTA thresholds and post treatment increases in serum lipids as well as ABR latencies when correlation tests were applied.

Regression analysis revealed that serum blood lipid levels are well predictors of shift in both PTA & ABR thresholds.

Discussion

All patients meeting the eligibility criteria were referred to the Audiology & Vestibular Clinic at Qena University hospitals. Only data from patients who consistently used oral isotretinoin for three months were included. Prior to and following oral isotretinoin therapy, pure-tone audiometry was conducted across frequencies ranging from 250 to 8000 Hz. Initial hearing thresholds fell within the normal range. However, significant differences in hearing thresholds emerged at frequencies of 3, 4, 6, and 8 KHz when comparing pre- and post-treatment values.

Similar findings were noted by **Akdağ et al. (2014)** in their study involving 31 acne patients treated with systemic isotretinoin. They observed significant changes in hearing thresholds at 1000, 2000, 4000, and 6000 Hz frequencies after 2 and 4 weeks of treatment. **Ugur et al. (2012)** investigated 23 acne vulgaris patients (46 ears) treated with high-dose systemic isotretinoin (5 mg/kg). They found bilateral hearing threshold changes following four months of treatment, despite insignificant levels of otoacoustic emissions amplitude.

The impact of isotretinoin on inner ear function in acne patients remains controversial. A commonly used measure in auditory brainstem response (ABR) assessments is the latency of component peaks, which provides robust and clinically relevant information. Our ABR latency measures remained within the normative range, yet significant differences were observed, particularly for waves I, III, and V (see tables 4 & 5). Wave I, reflecting cochlear blood flow, was closely monitored for latency shifts.

These results align with findings from **Nikiforidis et al. (1994)**, who reported increased latencies and interpeak latencies, as well as decreased amplitudes in severe nodulocystic acne patients following oral isotretinoin therapy. Conflicting data regarding isotretinoin's effects on the hearing system persist, possibly influenced by various factors such as timing of measurements during therapy and subjective nature of audiometric tests **(Halpin and Raugh, 2009; Bhattacharyya, and Megerian, 2011)**.

While pure-tone audiogram remains a reliable measure of auditory threshold, it does not offer a comprehensive assessment of auditory pathway damage. Notably, triglyceride and total cholesterol levels significantly increased before and after treatment, potentially contributing to hearing loss through hyperlipidemia-induced cochlear toxicity or reduced vascularization. High cholesterol levels

have been associated with a 33% higher risk of hearing loss.

Conclusion

In summary, oral isotretinoin may adversely affect human inner ears, possibly attributed to elevated serum blood lipids.

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