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Original Article

An Evaluation of Sensory Neural Hearing Loss in Thalassaemic Patients Treated with Desferrioxamine and Its Risk Factors

M. Sonbolestan MD[*], *F. Mokhtarinejad MD*[**], *M. Omrani MD*[**]

ABSTRACT

Back ground: In major thalassaemia patients who need blood transfusion, iron overload is a major therapeutic disadvantage that leads to heart failure which is the major cause of death in such patients. Desferrioxamine (DFO) is the most efficient factor for iron chelation, but it carries adverse effects such sensory-neural hearing loss.

Methods: The study began in March 2002 and continued untill March 2003, on 160 cases of thalassaemia to determine the incidence of sensory – neural hearing loss and its risk factors in patients who received Desferrioxamine (DFO). All cases underwent audiometric tests. Retrospectively, other needed information were either obtained through interview or extracted from the medical files. Results were analyzed with ANOVA, t-test and Chi-square tests.

Results: Seventy-six patients of the total 156 patients showed impairment in PTA (48.7%) with 24 of them suffering significant involvement (15.4%). These abnormalities generally affected high frequencies including, 4000 and 8000 Hz. Male gender, increased serum billirubin level and fasting blood sugar were statistically correlated with hearing loss (p.v = 0.038, p.v = 0.38, p.v = 0.002 respectively). There was no significant correlation between hearing loss and other factors. Mean DFO administration in patients, was 29.69 mg/kg/day and mean therapeutic index of DFO was 0.01 mg/kg/day/mg/lit. Both of them were below the critical level (<40mg/kg/day and <0.025mg/kg/day/mg/lit respectively), however hearing loss had developed.

Conclusion: Controlling DFO dosage per se does not seem to be enough for decreasing ototoxicity rate. Periodic audiometric tests are highly recommended to detect hearing loss as soon as possible. There are some other factors such as male gender, increased billirubin and FBS, which contribute to DFO ototoxicity. Looking for these risk factors and controlling them, would help identifying susceptible patients and preventing this complication.

Key words: Desferrioxamine (DFO), Sensory-neural hearing loss (SNHL), Thalassaemia therapeutic index (TI)

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Desferrioxamine (DFO or Desferal) is a natural metabolite of Streptomyces pilosus which has been introduced as an iron chelator in patients who develop iron overload since 1962. In cases of major thalassaemia, as a result of iron overload, heart failure occurs, which is the major cause of death in such patients. DFO still remains the most efficient factor to decrease iron overload in thalassaemia patients.

"Olivieri'' in 1986, demonstrated 22 cases of sensory neural hearing loss (SNHL) among 89 patients treated with DFO [1], besides, "Gallant'' in 1987 showed that SNHL in the study of Olivieri seemed to be highly does dependent[2]. Most of DFO related hearing losses involve high frequencies, like other ototoxic drugs; such as cis-platin and aminoglycosides [3]. In some cases, SNHL appears suddenly, but it can also present as asymptomaticly progressive.

* Associate Professor, Department of Otolaryngology, Isfahan university of Medical science, Isfahan, Iran
** Resident Assistant, Department of Otolaryngology, Isfahan university of Medical science, Isfahan, Iran
Correspondence to: Dr. Farhad Mokhtarinejad, No.82, Omoomi alley, Ordibehesht Street, Isfahan, Iran. P.O.Box: 81358-53531
E-mail: f_mokhtari_n@yahoo.com

With dose adjustment or cessation of DFO, many patients improve either relatively or completely over several weeks, but others need hearing aid for their SNHL [3, 4].

Many factors are mentioned as risk factors in various studies, however the two following factors seem to be most important:

1- The amount of DFO in relation to body weight**:** recommended dose is ≤40mg/kg/day.

2- DFO therapeutic Index (TI) which is measured with the amount of DFO dosage per weight on ferrittin level ratio. The recommended Index is less than 0.025 [5].

Incidence of DFO ototoxicity has been reported as ranging from 3.8% to 57% [3] but most reports ranged from 20% to 30% [4, 5, 6, 7]. In DFO ototoxicity, outer hair cells (OHC) seem to be the main target. One study showed that with low doses of drug, supporting cells are damaged at first, and with higher doses, OHC's are destroyed, too [8].

On the other hand, new studies revealed a protective effect for DFO against cis-platin and Aminoglycoside induced ototoxicity in animals [9, 10, 11, 12, 13].

This protective effect is related to the role of DFO in iron metabolism.

Iron-Aminoglycoside complex induces active oxygen radicals formation which destroy OHCs. DFO facilitates iron excretion, so decreases complex formation. DFO is considered a scavenger for free radicals [10]. The drug dosage in such studies were 100mg/kg, which is apparently higher than the recommended dosage (40mg/kg) [9, 10].

As a result, the effect of DFO dosage in ototoxicity by it self seems questionable and perhaps other factors such as constitutional factors like gender, genetics, and age or exogenous factors such as taking other ototoxic drugs interfere with DFO ototoxicity. This study was performed on 160 thalassaemic patients who received DFO and we evaluated SNHL, its risk factors and TI in them.

Subjects and Methods

This study was performed on 160 patients suffering major thalassaemia at "Sayed-Al-Shohada'' hospital, Isfahan, central Iran, from March 2002 to March 2003. Sampling was done using systematic randomization. In this hospital, laboratory tests such as serum levels of Na^+, K^+, Ca^{++}, Ph^-, FBS, Liver Function Tests (AST, ALT, Alk Ph), Thyroid Function Tests (T_4,TSH) and serum ferritin level were checked every 6 months, and the results were recorded in patients' files.

We performed audiometric tests including PTA, SRT and SDS for all patients. A data chart was completed using questionnaires and patients' files retrospectively. The information included age, gender, weight, DFO dosage, hearing complaints, if any, patient's compliance in taking DFO, and the results of periodic lab tests.

Exclusion criteria were:

A history of hereditary SNHL in the family.

A history of diseases or drug intake which could lead to SNHL. (like meningitis or use of Gentamicine)

A suspicious history of noise-induced hearing loss (NIHL).

COM or pathologic findings on ear examination.

A total of 4 cases were excluded despite suffering severe SNHL. Two cases had a history of meningitis, one of them had a history of COM and ear surgery, and the last had a history of sudden SNHL with a suspected history of mumps.

According to hearing ability of the worse ear for any of cases, they were put in 3 groups:

Group A: Patients with "significant'' changes on their PTA entered this group. Inclusion criteria for the cases in this group were having at least one of the following conditions in at least one ear:

1- A difference of 20 db or more between 2 sequential frequencies.

2- Hearing threshold > 40 db in at least one frequency.

Group B: This group included cases with "notable'' changes in their PTA. Their PTA showed difference compared to normal PTA, yet the differences were lower than in group A. At least one of the following conditions was found in at least one ear:

A difference of 10 db or higher(less than 20) between 2 sequential frequencies.

Hearing threshold 25 db or more but less than 40 db in at least one frequency.

Group C: Cases with normal PTA entered this group. Inclusion criteria were as follows in both ears:

Hearing threshold below 25 db in all frequencies.

Difference between 2 sequential frequencies below 10 db.
The collected data were analyzed with ANOVA, Chi-square and paired t-test.

Results

Incidence of hearing loss

From 156 cases, 24 patients (15.4%) had significant changes in hearing and were marked as group A. 52 cases (33.3%) showed notable changes in hearing evaluation, so were put in group B. The remaining 80 cases (51.2%) who developed no changes of hearing formed group C.

Inclusion Criteria

In group A, 23 cases (45.8%) had the 1st criterion (more than 20 db difference between 2 sequential frequencies), only one case (4.2%) entered the group with the 2nd criterion. 10 cases (41.6%) had both criteria.

In group B, 46 cases (88.5%) showed the 1st criterion (the difference between 2 sequential frequencies more than 10 db and equal with or less than 20 db) 6 cases (11.5%) had the 2nd criterion. The remaining 16 cases (30%) experienced both criteria.

Bilateral involvement

In group A, 9 cases (37.5%) had the criteria of significant hearing loss in both ears; but symmetrical pattern was found in 6 patients (25%). From the rest of the patients, 11 cases showed less but notable hearing impairment for meeting the criteria of group B in their better ears (45.8%). Thus, in 20 patients (83.3%) bilateral involvement was found. Only 4 cases had unilateral involvement.

In group B, 26 cases (50%) were involved bilaterally, and in 7 patients (12%) symmetrical pattern was found, others had a unilateral involvement.

SRT and SDS evaluation: After analyzing our data, no statistically significant differences were found between the 3 groups. (p.v=0.474, p.v=0.565, respectively)

PTA evaluation: No significant differences were found between the 3 groups after analyzing frequencies of 250Hz, 500Hz and 1000Hz. The difference in 2000Hz seemed to be notable and was significant in frequencies of 4000Hz and 8000Hz. (table 1, figure 1, 2)

4000Hz: Mean of right hearing threshold in group A was 16.87±14.12 db, in group B was 11.15 ± 8.20 db and in group C, it was 12.31±4.96 db (p.v=0.016). In the left ear, the results were 17.7± 5.32 db for group A, 10.48±8.53 db for group B and 12.87±5.61 db for group C (p.v = 0.004).

8000Hz: Mean of right hearing thresholds of groups A, B and C were measured as 22.91±12.59 db, 10.96±9.85 db and 12.87±5.49 db, respectively (p.v < 0.001). In the left ear the results were 23.12±16.6 db for group A, 12.5±9.26 db for group B and 12.81±5.14 db for group C (p.v < 0.001).

Therefore, DFO ototoxicity was generally associated with high frequency impairment. There was no significant difference between right and left ear.

Hearing complaints: No significant difference was found between the 3 groups in hearing complaints (hearing loss, tinnitus, aural fullness, etc.) (p.v=0.517). Most patients were asymptomatic in all 3 groups.

Risk factors

***1- Gender*:** From the total of 156 cases, 91 were male (58.3%) and 65 were female (41.7%). In the male group, 44 cases (48.4%) reported hearing loss and were placed in groups A and B. From 65 females, 32 (49.2%) had hearing loss. The incidence of hearing loss seemed to be equal in both genders, but hearing loss in the male gender was more severe. Nineteen cases of all 91 males (20.9%) but only 5 of the 65 females (7.7%) entered group A. The difference was statistically significant (p.v=0.038). So the severity of hearing loss was more evident with the male gender.

2- Age and weight: There were no significant differences among our groups regarding age and weight; (p.v=0.42, p.v=0.204 respectively)

***3- Anemia*:** No significant difference was found between the groups in the mean of hemoglobin (p.v=0.326).

4- *DFO Dosage:* Although mean DFO dosage in relation to body weight was higher in group A, the difference was not significant. The dose measured 32.63mg/kg for group A, 24.16 mg/kg for group B and 29.14 mg/kg for group C (p.v=0.167). Note that DFO dosage in all groups was apparently lower than the toxic level (40mg/kg).

5- *Patients'compliance:* It was described as questions asked from the patients and were expressed in percent, and analyzed among all groups. No significant difference was found (p.v < 0.436).

6- *Duration of DFO intake:* Mean duration of DFO administration for the groups A, B and C were 9.75± 4.46, 10.05± 5.10 and 8.82± 5.03 years, respectively. No significant differences seemed to exist (p.v=0.37).

7- *Serum ferritin level and DFO therapeutic Index (TI):* Serum ferritin level was checked on three separate occasions:

1- Ferritin level checked during last 6 month.

2- Mean of ferritin levels during last year.

3- Mean of all ferrittin levels charted in patient's file.

Therapeutic index (TI) was evaluated, too.

$$TI\left(\frac{mg/kg/day}{\mu g/lit}\right) = \frac{DFO\ (mg/kg/day)}{Ferritin\ \ (\mu g/lit)}$$

In none of the patients significant difference between serum ferritin levels was found (p.v=0.268, p.v=0.143, p.v=0.203 respectively). Besides, TI of the 3 groups in those times did not show a significant difference, either (p.v=0.863, p.v=0.707, p.v=0.767 respectively). Note that TI in all the 3 groups was evaluated between 0.008 to 0.011, which was apparently lower than the toxic amounts (>0.025).

8- *Serum electrolytes:* No significant difference was found between serum levels of Na^{+}, K^{+}, Ca^{++}, and Ph^{-} in the 3 groups. (p.v=0.175, p.v=0.352, p.v=0.659, p.v=0.679 respectively).

9- *Blood sugar:* Mean of FBS was measured 107± 44 mg/dl, 91± 9 mg/dl and 90±10 mg/dl in groups A, B and C, respectively. A significant difference was observed between the groups and FBS in group A was notably higher. (p.v=0.002)

10- *Billirubin and LFT*: Although higher serum levels of liver enzymes (AST, ALT and Alk Ph) were found in the groups with a more severe hearing loss, the difference was not statistically significant (p.v=0.108, 0.425 and 0.335, respectively). On the other hand, mean billirubin level in groups A and B were measured as 1.63mg/lit and 1.67mg/lit respectively, while it was 1.38mg/lit in group C. Patients with hearing loss, had higher Billirubin levels and the difference was significant. (p.v = 0.038)

11- *Thyroid tests:* No significant difference was found between mean T_4 and TSH levels between the 3 groups (p.v = 0.594, p.v = 0.064, respectively).

Tables 1. Comparison of mean of hearing threshold levels among 3 groups

Hearing threshold (dl) / Frequency (Hz)		Group A		Group B		Group C		Total		P.V
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
250	R	13.95	7.36	17.21	9.62	14.87	5.51	15.51	7.45	0.114
	L	12.50	8.07	14.13	6.91	14.50	5.56	14.07	6.54	0.423
500	R	11.66	6.19	14.80	8.22	13.62	5.15	13.71	6.52	0.147
	L	11.66	7.49	11.73	6.25	13.50	5.11	12.62	5.94	0.171
1000	R	10.83	5.03	10.28	7.63	11.56	4.10	11.02	5.64	0.443
	L	10.41	6.41	9.80	6.63	11.06	5.07	10.54	5.83	0.482
2000	R	10.20	7.58	9.23	7.50	11.87	4.73	10.73	6.31	0.056
	L	13.12	12.49	9.03	7.41	11.43	6.01	10.89	7.85	0.073
4000	R	16.87	14.12	11.15	8.20	12.31	4.96	12.62	8.23	0.016
	L	17.70	15.32	10.48	8.53	12.87	5.61	12.82	8.96	0.004
8000	R	22.91	12.52	10.96	9.85	12.87	5.49	13.78	9.32	<0.001
	L	23.12	16.60	12.50	9.26	12.81	5.41	14.29	9.84	<0.001

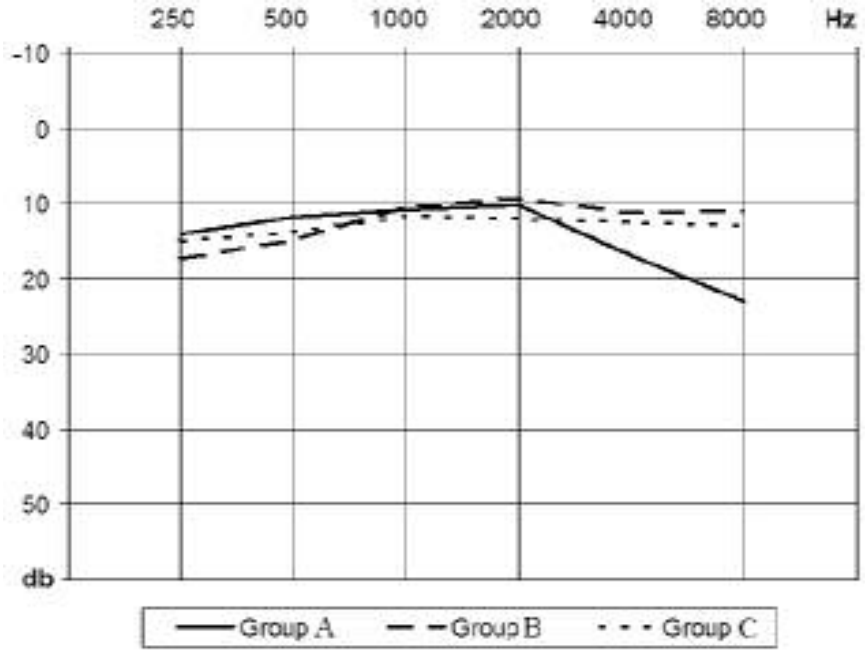

Figure 1. Comparison of mean of hearing threshold among the 3 groups in right ear

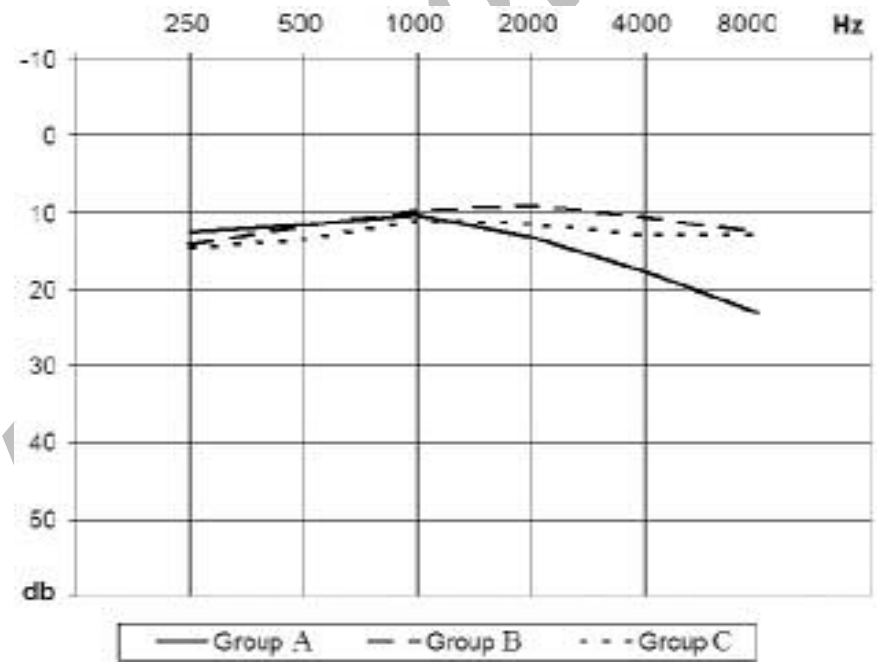

Figure 2. Comparison of mean of hearing threshold among the 3 groups in left ear

Discussion

The incidence of hearing loss was estimated to be 48.7%. About 15.4% of the cases, (group A), showed severe changes in their PTA tests and others (33.3%) had lower changes (group B). Thus, the incidence of hearing loss in our study was found to be between 3% and 57% [1],

while in most studies, an incidence range of 20%-30% was reported for hearing loss [4, 5, 6].

The more severe the hearing loss was, the higher the risk for bilateral involvement rose. In 83.3% of the cases of group A, a bilateral involvement was found, but about 50% of the cases in group B showed bilateral hearing impairment, however, symmetrical changes were found occasionally (only 25% of group A and 12% of group B). Kanno also reported the impairment as an asymmetric one [3].

No significant difference was found between right and left ears, just similar to previous studies. The most common frequencies involved, were 4 and 8 KHz. The studies by Olivieri, Guerin, Kanno and Styles revealed a high frequency involvement in the ototoxicity of DFO too [1, 2, 3, 4]

No significant correlation was found between hearing complaints and hearing loss. This may be due to the involvement of high frequencies caused by ototoxicity on the early stages, thus the cases remain asymptomatic. In this study, no correlation was found between hearing loss and weight, age, patient cooperation, duration of DFO intake, and the severity of anemia. Most of the previous studies presented the same results, except one study which reported an increasing hearing loss with early ages and patient's compliance.

The incidence of hearing loss was equal between both genders, but its severity was significantly higher in the male gender. Other studies did not report any differences in the incidence of hearing loss or its severity between the genders [3, 4, 5, 6].

In this study there was no correlation between hearing loss and DFO with respect to body weight, serum ferritin level and DFO therapeutic index. In a prospective study by Styles and Vichinsky, no relations were found either [4]. DFO dosage in that study was below 50mg/kg/day but 29% of patients had an abnormal audiogram and no significant correlation was found between hearing loss and age, DFO dosage or duration, ferritin levels and DFO therapeutic index. It is considered that amounts of DFO > 40mg/kg/day and therapeutic Index > 0.025 serve as risk factors for hearing loss. Note that all cases of this study received 29.4 to 32.63mg/kg/day DFO and therapeutic index was between 0.008 and 0.011, both of them notably lower than the toxic levels, yet many of them were affected by DFO ototoxicity.

Conversely, Sha et al., Watanab et al. song BB et al. and Colon et al. separately used DFO to decrease the ototoxic effects of Aminoglycosides and Cis-platin in their animal studies and reported notable results [9, 10, 11, 12]. It is important that the dose of DFO in their studies was 100mg/ kg/day.

Thus, these evidences make the role of DFO dosage and DFO therapeutic index, questionable. Probably, other factors are more effective than DFO dosage in causing ototoxicity.

In this study, a significant relation was found between hearing loss and a high FBS and billirubin level. If confirmed by future studies, FBS and serum Billirubin may be used for identification of more sensitive cases which are at higher risk of DFO ototoxicity. Keeping the dose of DFO below 40mg/kg/day and therapeutic index lower than 0.025 did not seem enough for protecting against hearing loss. Thus, periodic audiometric evaluation is recommended for early diagnosis of hearing loss. Otherwise, male gender, increased serum billirubin, and a raised FBS are factors that seem to increase the risk of DFO ototoxicity. DFO dosage and TI roles in ototoxicity are questionable and maybe influenced by other factors.

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