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Conventional audiometric screening for detection of drug induced hearing loss in thalassemics: a pilot study

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ABSTRACT

Background: Drug induced hearing impairment is likely in subjects undergoing multiple blood transfusions which necessitates timely detection and rehabilitation, especially in the pediatric age group.

Methods: A total 30 thalassemic patients undergoing regular iron chelation therapy with Desferrioxamine and Deferasirox were included in this prospective study. Follow up studies were conducted after 12 months of chelation therapy i.e. after 1 year thus spanning a total duration of 1 years.

Results: The most common age group was 4-8 years (46%) followed by 8-12 years (20%). Male patients outnumbered female patients in the ratio of 2.75:1 constituting 73% of study population oral Deferasirox (80%) followed Desferrioxamine (13.3%) and a combination therapy (6.6%). The distribution shows shift of pure tone average in higher thresholds with continuation of therapy.

Conclusion: Despite Desferrioxamine doses usually felt to be low risk for ototoxicity (less than 40 mg/kg/day), found a high rate of ototoxicity in our patients using pure tone audiometry (23%).

Keywords: Blood transfusion, Hearing impairment, Pure tone audiometry, Thalassemia

INTRODUCTION

Thalassemia's are a group of disorders characterized by deficient production of hemoglobin due to decreased synthesis of one of its constituent globin chains. Thalassemia is the most commonly inherited disorder worldwide with a particularly high incidence in Punjab. Over 180 million people in the world and over 20 million people in India carry the thalassemia gene. Prevalence of β -thalassemia trait in India is 3% in the general population but among certain communities like Punjabis the incidence of β -thalassemia trait ranges between 8-15%. $^{\rm I}$

Patients with thalassemia usually develop anemia within the first six months of life because the decreasing levels of fetal hemoglobin cannot be replaced by normal adult hemoglobin.

These patients thus require lifelong blood transfusions which serve two main purposes:

- 1. Maintenance of adequate hemoglobin concentration.
- 2. Suppression of defective hemoglobin synthesis in the bone marrow.

If regular transfusion therapy is not initiated a clinical picture of severe untreated β -thalassemia develops characterized by profound anemia, splenomegaly and progressive bone marrow expansion. Over the last 3 decades, regular blood transfusion therapy has dramatically improved the quality of life and increased

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life span in these patients. Today in developed countries the life expectancy of these patients varies between 25 and 55 years, depending on compliance with medical treatment.

However, with current transfusion regimens, iron overload and other transfusion related complications are the main concerns as there is no mechanism in the body to excrete the excess iron. Hence the only way to remove this excess iron from the body is by chelation therapy which is also, therefore, lifelong.

However, chelation therapy itself is associated with potentially debilitating multisystem side effects like growth retardation, ototoxicity, ocular toxicity and skeletal deformities.

Ototoxicity is one such side effect which, if detected early and with dose adjustments, can be prevented iron chelation therapy in thalassemic patients is started after about 10 to 20 blood transfusions have been administered or when S. ferritin levels are more than 1000 ng/ml. The agents used for chelation therapy are-

- Desferrioxamine (Desferal)
- Deferasirox (Asunra) and
- Deferiprone (Kelfer)
- Combination of 1 and 3.

Thalassemics are vulnerable to auditory abnormalities due to the disease (thalassemia), the treatment (repeated transfusions and iron overload) as well as treatment of iron overload (chelation therapy) either independently or in synergism chelation therapy induced ototoxicity being the most significant.

Among these are the iron chelating agents, Desferrioxamine and Deferasirox.

It is not easy to foresee how severe ear damage could be in each patient undergoing chelation therapy, so it is important to monitor these patients by serial pure tone audiometric examinations to detect the first signs of ototoxicity.

Pure tone audiometry is not reliable in children <3 years of age because it is a behavioral method of evaluation, thus otoacoustic emissions and Brainstem evoked studies are carried out in this age group.

Aims and objectives of the study were to assess the prevalence of ototoxicity in multiple transfused thalassemic patients on regular chelation therapy (with Desferrioxamine and Deferasirox), to assess the progression of hearing loss in children and young adults with β -thalassemia major and to correlate ototoxicity with age, sex, dose and duration of chelation therapy, Therapeutic index.

METHODS

Patients

30 Thalassemic patients undergoing regular iron chelation therapy with Desferrioxamine and Deferasirox at Dayanand Medical College and Hospital, Ludhiana (Punjab) were included in this prospective study. Follow up studies were conducted after 12 months of chelation therapy i.e. after 1 year thus spanning a total duration of 1 years.

Inclusion criteria

Thalassemic patients in the age group of 3 years to 25 years undergoing regular iron chelation therapy (with Desferrioxamine and Deferasirox or a combination of either with other non-ototoxic drugs).

Research design

The study was an observational study with no intervention in the diagnostic and therapeutic management. It was designed as a prospective study with a follow up audiometric evaluation after 12 months of first assessment.

Chelation regiment

Thalassemia patients are transfused monthly to maintain their hemoglobin level between 9 and 10.5 g/dL.

Age

The average age of the group was 120 months/ 10 years with minimum age being 44 months/3.6 years and maximum age being 21.5 years.

Sex

A total 8 females and 22 males were selected for inclusion in the study.

Therapy

Of the 30 patients, 24 were on Asunra (Deferasirox), 4 on Desferal (Desferrioxamine) and 2 on a combination of both.

Test environment

Pure tone audiometry was performed in standard sound treated two room set up, with noise levels within permissible limits according to ANSI (1977) Standards for Maximum Permissible Ambient Noise levels.

Measurement of PTA thresholds

Pure-tone audiometry was conducted using the commercial audiometer Arphi 2009 and the audiometric headphones telephonic TDH39 with tone stimulus ranging from 0.25 to 8 kHz (0.25, 0.5, 1, 2, 4 and 8 kHz) and BC thresholds with bone vibrator B-70 with tone stimulus ranging from 0.25 to 4 kHz (0.25, 0.5, 1, 2 and 4 kHz) using the standard modified Hughson-Westlake technique.

RESULTS

30 patients who passed the inclusion and exclusion criteria were selected for the study.

Table 1: Age distribution of subjects.

Age (months)	Age (years)	No. of patients	Age of patients (%)
0-48	0-4	1	3
49-96	4-8	14	46
97-144	8-12	6	20
145-192	12-16	3	10
193-240	16-20	4	13
241-268	20-24	2	6.6
Total		30	100

The average age of the group was 120 months/ 10 years with minimum age being 44 months/3.6 years and maximum age being 21.5 years.

The most common age group was 4-8 years (46%) followed by 8-12 years (20%).

Table 2: Sex distribution of subjects.

Sex	No. of patients	Age of patients (%)	Patients with hearing loss	Patients without hearing loss
Male	22	73.3	11	11
Female	8	26.6	3	5
Total	30	100	14	16

In our study, the male patients outnumbered female patients in the ratio of 2.75:1 constituting 73% of study population.

Table 3. Type of chelation therapy.

Chelating Agent	No. of patients	Age of patients (%)
Desferrioxamine only	4	13.3
Deferasirox only	24	80
Combination	2	6.6
Total	30	100

of the two ototoxic chelating agents, the majority of patients were on oral Deferasirox (80%) followed Desferrioxamine (13.3%) and a combination therapy (6.6%).

Table 4: Duration of chelation therapy.

Duration of chelation (months)	No. of patients	Age of patients (%)
0-10	3	10
11-20	2	6.6
21-30	11	36.6
31-40	12	40
41-50	0	0
51-60	1	3.3
61-70	0	0
71-80	1	3.3
Total	30	100

Duration of chelation therapy was taken from the start of chelation therapy till the Follow up observation. The majority of patients in our study have been on chelation therapy for 31-40 months period (40%) followed by 21-30-month period (36.6%) with on patient having completed 80 months of chelation therapy.

Table 5: Pure tone average threshold distributing at first and follow-up observation.

Pure tone average (dB)	No. of patients First observation	Follow-up observation
5-10	5	0
11-15	17	14
16-20	5	7
21-25	1	2
26-30	2	6
31-35	0	1
Total	30	30

Pure tone average was calculated in patients on chelation therapy as average of hearing threshold at 2, 4 and 8 kHz at both First observation and follow up observation. The distribution shows shift of Pure tone average in higher thresholds with continuation of therapy. The number of patients with Pure tone average above 25 dB which was taken as hearing deficit threshold have increased from 2 (6.6%) at the start of study of 7 (23.3%) on Follow up observation.

This shows that primarily affects the higher frequencies.

DISCUSSION

The characteristics of chelation therapy induced ototoxicity are insidious in onset; bilateral, but unilateral hearing loss have been reported; cause high frequency sensorineural hearing loss i.e. there is a 'cochleotopic'

gradient of susceptibility so that the basal region of the cochlea is damaged earlier and at lower doses than the apical region; occasionally reversible with dose reduction.

The reported incidence of sensorineural hearing loss in transfusion dependent patients receiving Desferrioxamine varies from 3.8% to 57%. Using pure tone audiometry, the prevalence of hearing deficit in our study group was found to be 23% similar to 29% in the Styles and Vichinsky study, 20% by Liang et al 27 to 44% by Mehran Karimi et al study and 20.2% in the Kontzoglou G et al study, Chiodo et al too in 1997 reported hearing loss in 29% (22/75) of their patients on Desferrioxamine using PTA.¹⁻⁵

Compensatory bone marrow expansion has been found to be associated with higher incidence of CHL (canal atresia) and SNHL (nerve compression). Increased incidence of adenoid hypertrophy has also been reported which predisposes to OME iron overload (high mean S Ferritin levels) have been shown to be associated with higher incidence of SNHL.

Hemochromatosis has been reported to be associated with higher incidence of cholesteatoma.

Chelation therapy with Desferrioxamine and Deferasirox has myriad systemic side effects with proven ototoxicity leading to SNHL.

The mechanism of toxicity of Desferrioxamine and Deferasirox for the eyes and ears and ears remains unclear. It has been suggested that Desferrioxamine reacts with superoxide free radicals to form a relatively stable nitroxide-free radical that reacts with methionine, cysteine, glutathione, vitamin C, and alcohol dehydrogenase, causing a loss of enzyme activity.

Triantafyllou et al conducted a brainstem auditory evoked potential (BAEP) study in thalassemic patients receiving chronic treatment with desferrioxamine.⁶ These abnormalities were found to be related to the formation of wave I or the prolongation of its latency, suggesting a cochlear disturbance rather than auditory nerve toxicity.

But they did not employ DPOAEs as screening tool.

Characteristics of auditory involvement

On PTA analysis, our study reveals a significant decrease in threshold value at frequencies of 2000, 4000 and 800 Hz but not at lower frequencies of 250,500 and 1000 Hz. The findings in both ears were almost identical 6 patients (20%) had hearing loss less than 30 dB while 1 patient (3.33%) had loss between 30 and 35 dB. The study also revealed progression of hearing loss at higher frequencies with continuation of therapy.

A high percentage of patients also show abnormalities at 1000 Hz which could be attributed to the ambience noise.

Chiodo et al also reported a high-frequency sensorineural hearing loss in their patients with 33% (7/21) having a notch at 6 kHz. Kontzoglou G et al also reported a high frequency hearing loss in such patients.^{4,5}

Ambrosetti et al reported similar findings. 26% patients reported a high frequency SNHL with 22.8% below 35 dB and 6.6% between 35- and 75-dB hearing loss.⁷

Effects of various management parameters on hearing loss

In 1986 Olivieri et al reported that patients with auditory and visual effects were younger, had lower ferritin values, and were receiving higher doses of deferoxamine than those who were unaffected.⁸ Similar findings were reported by Albera et al.⁹ They reported that hearing loss appeared to be correlated with younger age, peak Desferrioxamine doses and lower iron load.

Porter et al described risk factors for Desferrioxamine ototoxicity, which include a dose more than 35 mg/kg per 24 hours for at least 3 months and a serum ferritin level of less than 2000 ng/ml. An iron overload was considered protective against ototoxicity. Low iron overload may result in an increase in iron-free Desferrioxamine available to chelate trace metals like Zn in the cochlea. This may lead to inhibition of key metalloenzymes such as tyrosinase or lipoxygenase within the cochlea leading to OHC damage.

However subsequent studies have found no association between age or ferritin levels and ototoxicity.

Safe dose to prevent ototoxicity

The recommended dose of Desferrioxamine is 20-60 mg/kg/day with maximum of 50 mg/kg/day and for Deferasirox is 20-40 mg/kg/day.

A dose less than 50 mg/kg/day has been conventionally considered low risk for ototoxicity.

Timing of auditory assessment

Karimi et al have recommended routine and periodical audiologic assessment at least once every 2 years using PTA for a prompt diagnosis and management of hearing complications.³

Based on these findings, we stress the need for regular audiological testing for all patients on chelation therapy and feel no dose of chelation therapy is "safe" from the development of ototoxicity.

Resolution of ototoxicity with dose reduction

Thus, serial audiometric evaluations would help in detecting chelation induced hearing loss and may prevent permanent damage created by long term high dose therapy. However, the effect of dose reduction on resolution of ototoxicity was not analyzed in our study which was purely an observational study.

Limitations of study

The number of patients is small. Most of the patients were already on chelation therapy at the start of the study. So pretherapy baseline audiological status was not known. This was a purely observational study with no attempt being made to change the management course. The effect of dose reduction on auditory function improvement was not studied.

CONCLUSION

Despite Desferrioxamine doses usually felt to be low risk for ototoxicity (less than 40 mg/kg/day), found a high rate of ototoxicity in patients using pure tone audiometry (23%). Some previous studies have shown a correlation between ototoxicity and dose, duration or therapeutic index of chelation therapy. However, no variables were identified in this study that reliably predict ototoxicity. Which impress on the need for at least regular audiological screening using conventional pure tone audiometry for early detection of ototoxicity where facilities for otoacoustic emissions and evoked response audiometry are not available.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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