Desferioximine induced Ototoxicity in Thalassemic patients

Dharam Vir[1], N. K. Panda[2], R. K. Marwaha[3]

[1]Speech and Hearing Unit, [2]Department of Otolaryngology, [3]Department of Pediatrics, Advanced Pediatric Centre, Post Graduate Institute of Medical Education & Research Chandigarh (160012), INDIA

KEY WORDS

Thalassemia
Desferioximine
Injection therapy
Oral therapy

Corresponding Author:

Dharam Vir MSc
Tel. : +911722756954
E-mail : vir64@gmail.com

ABSTRACT

Background: Thalassemia is a hereditary disorder requiring regular blood transfusion. **Purpose:** To determine hearing sensitivity in transfusion-dependent thalassemics who were receiving desferioximine and on oral iron chelation (desferioximine) therapy. **Methods:** 26 patients with B-thelassemia in the age range of 5-22 years were enrolled in the thalassemia transfusion unit in the Advanced Pediatric Center of Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. The patients to be enrolled in this study were randomly selected. **Results:** It was observed that the hearing deteriorated in patients who were given injected desferioximine whereas it fell within normal limits in case of those who were given oral iron chelation therapy. **Concluson:** This study confirms the necessity of regular audiological monitoring during the course of the disease.

doi : 10.5214/ans.0972.7531.1017407

Introduction

β- Thalassemia is a major chronic hereditary disorder, which usually manifests with severe anemia in infancy. These patients receive regular red cell transfusion at intervals of 3-4 weeks to sustain life. The repeated transfusion and the basic disease results in an iron overload state with consequent complications of cardiac / liver failure in the second or third decade of life.

Iron chelation therapy with desferioximine removes excess iron and helps to prevent organ damage in patients receiving regular erythrocytes transfusion. Until recently, desferioximine was considered generally free from major side effects. Clinical and sub-clinical studies have shown that visual and auditory neurotoxicity was present in about one and a half of the patients receiving subcutaneous infusions of desferioximine.[1] An oral iron chelator, deferiprone was evaluated in multicentric study in the early 1990's. Efficacy in reducing/preventing iron overload was documented in most patients. The cost is less than one fifth of the cost of desferioximine and hence making it more affordable.

The only curative treatment available is bone-marrow transplant (BMT) which is possible only if a matched HLA sibling donor is available. The cost of a BMT in India is approximately Rs. 9.0 lacs, an expense that is beyond the reach of almost 95% of the patients.

The major side effects which have been observed in patients receiving oral iron chelation are musculoskeletal pain (25-30%) and severe neuropaenia (1-2%). The aim of this study was to determine auditory sensitivity changes in the patients receiving desferioximine and oral chelator-deferiprone and to correlate the threshold differences in relation to duration of iron chelation therapy.

Methods

Patients with β- Thallasemia referred for blood transfusion in the Advance Pediatric Centre, PGIMER, Chandigarh who came to Speech and Hearing Unit of Otolaryngology Department were included in this study. The patients enrolled in this study were randomly selected according to the following criteria and informed consent was obtained:

Inclusion criteria

1. Patients requiring diagnosed cases of β- Thalassemia.
2. Patients requiring multiple red cell transfusion manifested in infancy.
3. Patients receiving injected iron chelation therapy (Desferioxamine) or defriprone for a period ranging from 0-3 years.
4. Patients receiving oral iron chelation therapy (defriprone) for a period ranging from 0-6 years.

Exclusion criteria

1. Post- transfusion age -18 months.
2. Overt evidence of serious infection.
3. Neurological deficits, history of seizures.
4. Those suffering from CSOM, and
5. Hearing impairment.

Total number of subjects was 26 (19 males and 7 females). 8 patients were on injectable desferioximne while 18 were on oral iron chelation therapy. These patients were visiting Advanced Pediatric Centre of Post Graduate Institute of Medical Education and Research, Chandigarh, in the Thalassemia clinic for regular blood transfusion and were referred to the Speech and Hearing Unit of the Department of Otolaryngology and Head and Neck Surgery where the brief history of these patients was taken with reference to past, present and recurrent hearing disturbances. Objective examination of external auditory meatus and tympanic membrane was performed and all the audiological testing was done in the sound treated rooms of Speech and Hearing Unit of the same department.

1. A thorough evaluation of the patients was carried out in the Department of Otolaryngology, which included history, clinical examination and hearing evaluation.
2. The hearing assessment was done at different octave frequencies, *i.e.*, 250 Hz, 500 Hz, 1 KHz, 2 KHz, 4 KHz, and 8 KHz, using an Amplaid 309 – Audiometer.
3. Normal hearing was defined as threshold sensitivity equal to or less than 26 dB hearing threshold level (ANSI-1969).

Results

The sample characteristics of the homozygous β- Thalassemia for iron chelation therapy is given in Table-1.

Table 1: Sample Characteristics of thalassemic patients

No of patients	Age Range	Sex	
52	5-22	M	F
		38	14

Table 2: Thresholds of hearing sensitivity in patients receiving Oral/ Injected iron chelation therapy n = 52 (0-3 yrs)

Frequencies H_2

Freq.(Hz)	250	500	1k	2k	4k	8kH_z
Intensity (oral) in dB	20.18	19.52	20.41	27.33	32.74	35.27
Intensity (Injected).	15.85	19.64	14.77	21.49	33.74	35.50

Freq = Frequency

Table 3: Threshold of hearing sensitivity changes with different dosages of oral/iron chelation therapy on thalassemia patients (0-6 yrs) n = 52

Freq.	250	500	1k	2k	4k	8k
Intensity (oral) in dB	18.46	15.55	16.66	14.16	12.83	17.49
Intensity (Injected)	19.52	19.27	17.18	25.37	48.91	33.05

Freq = Frequency

Table-2 shows the hearing thresholds of Oral/injected deferioximine. Mean threshold increase was observed at octave intervals *i.e.,* 250 to 8000 Hz during 0-3 years of treatment.

Table-3 shows that the mean hearing threshold increased in patients receiving injectable iron chelation therapy only but the hearing thresholds of the patients receiving oral iron chelation therapy decreased and almost came under the normal values as per the ANSI 1969 standards for 0-6 years period.

The present study revealed that those Thalassemia patients who received injectable iron chelation therapy for 3 years had lesser deterioration of hearing threshold as compared to those who received therapy for 6 years. These results were nearly similar to the results obtained by Styles *et. al.*[2] They had done serial audiograms with chronically chelated patients over a period of 5 years.

However, those who received oral iron chelation therapy for 3 years had hearing impairement but by the time, they received therapy continuously for 6 years they became audiologically within normal limits which is in accordance with the long - term treatment of transfusion iron overload with the oral iron chelation deferiprone.[3]

Discussion

The iron chelated desferioximine was introduced more than 30 years ago[4,5] and remains the only chelator approved for regular use in North America and the only first-line agent approved for use in Europe. Desferioxamine improves hepatic, cardiac and endocrine dysfunction and lengthens survival in patients with iron overload.[6-8] The disadvantages include high cost[9] the requirement for daily parental administration and local and systemic toxic effects that include visual[10] and auditory neuro toxic effects[1] skeletal abnormalities[11] and growth retardation.[12]

The present study reveals that percentage of normal hearing at low frequencies and impairment at high frequencies is only 8% and 12% at 4 KHz and 8 KHz respectively. Therefore, it can be stated that hearing is affected at higher frequencies to some extent. These results are quite similar to another study done by Cohen *et. al.*[13] Shirane and Harrison[14] also reported similar findings that cochlear action potential threshold elevated from 20-40 dB and were most evident in high frequency region which is in agreement with the present findings. They examined the effect of desferoximine mesylate and hypoxia on the cochlea in Chinchillas. They administered the desferioximene mesylate, 100 mg/kg/day for five days/week intramuscularly to 19 Chinchillas for three months. They reported no changes in cochlea in chronic experiment scheduled to be similar to the clinical long-term chelation therapy but on the other hand acute administration of desferioximene gives rise to respiratory suppression accompanied by impairment of cochlear function and histological changes of sensory epithelium. The functional and histological damage to the cochlea is in the form of cytoplasmic protrusions and disarrangement of sensory hair cells at the level of inner hair cells, leaving outer cells mostly intact. It was also observed in acute experiments that a close correlation was also present between respiratory suppression and desferioximine mesylate. They concluded that it had very little direct toxic effect on cochlea and cochlear hypoxia seemed to be have been largely responsible for damage to sensory epithelium in acute experiments.

In another experiment Kimura *et. al.*[15] found that it interrupted the blood flow to the cochlea of Guinea pigs and it was observed that degenerative changes occurred in the cochlea. They also reported that inner hair cells are affected first and cell degeneration spreads to the outer hair cells. In other publication like Fernandez *et. al.*[16] Jordan *et. al.*[17] and Theopold[18] it was reported that post mortem changes in the sensory epithelium occur at the level of inner hair cells and then spreads to the outer hair cells. The histopathological changes in the cochlea were described in the above reports, which seem to be responsible for hearing impairment in thalassemic patients receiving the drug desferioximene and iron chelation deferioxamine at higher frequencies as observed in the present study.

Conclusion

The patients with β- Thalassemia receiving injectable and oral iron chelation therapy need to be followed up for regular audiological monitoring to detect any early changes in the hearing. A larger sample of data and the longer follow up *i.e*. 6-9 months would help us to reach a definite conclusion.

Competing interests – None, Source of Funding – None

Received Date : 02 July 2010; Revised Date: 27 August 2010

Accepted Date : 13 September 2010

References

1. Oliveri NF, Buncic JR, Chew E, *et al.* Visual and auditory neurotoxicity in patients receiving subcutaneous desferioxamine infusions. N Enl J Med 1986; 314: 869–73.
2. Styles LA and Vichinsky EP. Ototoxicity in haemoglobinopathy patients chelated with desferoxamine. J Pediatric – Haematoloncol 1996; 18: 42–45.
3. Kersten MJ, Lange-r Smeets ME, Verugdenhil G, *et al*. Long-term treatment of transfusional iron overload with the oral iron chelation deferiprone (L1): a Dutch multicenter trial. Ann – Haemtol 1996; 73(S): 247–52.

4. Sephon-Smith R. Iron excertion in thalassaemia major after administration of chelating agents. BMJ 1962; 1577–80.
5. Barry M, Flynn D, Letsky E, *et al*. Long - term chelation therapy in thalassaemia major: effect on liver iron concentration, liver histology and clinical progress. BMJ 1974; 2: 16–20.
6. Brittenham GM, Griffith PM, Nienhuis AW, *et al.* Efficacy of disferioxamine in preventing complication of iron overload in patients with thallasemia major. N Engl J Med 1994; 331: 567.
7. Modell B, Letsky EA, Flynn DM, *et al*. Survival and desferioxamine in thalassaemia major. BMJ 1982; 284: 1081.
8. Wolfe L, Oliveri N, Sallan D, *et al.* Prevention of cardiac disease by subcutaneous desferioxamine in patients with thalassaemia major. N Engl J Med 1985; 312: 1600–03.
9. Karnon J, Zeuner D, Brown J, *et al*. Lifetime treatment costs of beta-thallasaemia major. Clin Lab Haematol 1999; 21: 377–85.
10. Arden GB, Wonke B, Kennedy C, *et al*. Ocular changes in patients undergoing long–term desferioximine treatment. Br J Opthalmol 1984; 68: 873–77.
11. Brill PW, Winchester P, Giardina PJ, *et al*. Desferioxamine – induced bone dysplasia in patients with thalassemia major. Am J Roentgenol, 1991; 156: 561–65.
12. DeVirgiliis S, Congia M, Frau F, *et al.* Desferoxamine-induced growth retardation in patients with thalassemia major, J Pediatric 1988; 113: 66–69.
13. Cohen, A Martin, M Mizanin J, *et al*. Vision and hearing during desferoxamine therapy. J Pediatric 1990; 117: 326–330.
14. Shirane M and Harrison RV. The effect of defroxamine mesylate and hypoxia on the cochlea. Acta Otolaryngol 1987; 104: 99–107.
15. Kimura R and Perlman HB. Arterial obstruction of the labyrinth. Ann Otol Rhinol Laryngol 1958; 67: 5–40.
16. Fernandez C. Postmortem changes on the vestibular and cochlear receptors (guinea pig). Arch Otolyngol 1958; 68: 480–87.
17. Jordan VM, Pinheiro ML, Chiba K, *et al*. Postmortem changes in surface preparations of the cochlea Ann Otol Rhinol Laryngol 1973; 82: 111–25.
18. Theopold HM. Postmortem changes of fine structure in the auditory pathways (Organ of Corti and nuceous cochlearis of the guinea pig). Laryngol Rhinol (Stuttg) 1977; 56: 207–15.