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Interventional Study of Bone Mineral Density in Multi-Transfused Thalassemia Patients in a Tertiary Care Hospital

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Abstract
Background*: Patients with transfusion dependent thalassemia (TDT) are susceptible to osteopenia and osteoporosis due to various factors. There are various studies regarding efficacy of bisphosphonate in treatment of osteoporosis in thalassemia but there still no established protocol for the management of osteoporosis in thalassemic patient. The aim of this study is evaluation of a simplified regimen based protocol in improvement of bone mineral density and improvement in quality of life of TDT patients.*
Materials and methods*: It is an prospective, interventional study conducted over a duration of 1 year in TDT patients attending G.G.G. hospital for regular blood transfusion. After clearance from the ethical committee and consent from the parents, a total of 42 patients were enrolled according to inclusion criteria. Patients were scanned for Bone Mineral Density (BMD) and various biochemical tests were run. Participants were given treatment as per pre determined regimen. DEXA scan and few biochemical investigations in few patients were repeated. Results were analyzed with the help of standard statistical tests.*
Results*: Out of total 42 patients, before intervention, 19 patients were osteopanic and Rest 23 patients were osteoporotic. After intervention, 15 patients remain in osteoporotic range, 18 patients fall in to range of osteopenia. 9 of the enrolled patient had their DEXA scan report more than -1. Mean Z score before intervention is -3.0 ; Range -1.2 to -5.2 (SD = 1.20) . Wheare as mean Z score in after intervention is -2.11 ; Range 0.9 to -5.7 (SD = 1.44). By applying paired t test, the improvement of bone mineral density after intervention is found to be statistically significant (P value 0.0000556,< 0.01) t value = 4.49.*
Conclusion*: Evaluating BMD annually in TDT patients helps to prevent and intervene timely and appropriately. Administration of bisphosphonates, calcium, vitamin-D supplements, hormone replacement therapy (HRT), bone forming agents and newer therapies will help to improve bone mass. Changing lifestyle with mild daily exercise, appropriate diet, regular iron chelation therapy, early diagnosis and treatment of endocrine insufficiency and regular blood transfusions can help to achieve an optimal bone density in these patients. Use of this simplified regimen not only improve bone mineral density of the patients, will be helpful to decrease morbidity due to osteoporosis to a significant level.*

Keywords*: Thalassemia, bone mineral density, bone loss treatment, bisphosphonate.*

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I. Indroduction:-

Osteoporosis is highly prevalent and one of the major co – morbidity in a patient suffering from thalassemia major. The study will allow a simplified protocol to be established for better management of thalassemic patients. By timely and appropriate management, this will not only decrease risk of developing bony deformities and fractures but also improve overall quality of the life. Outcome of the results will help to add in the prevail knowledge and provide insight in the management of osteoporosis in thalassemia patient and also create data for policy makers to create a firm protocol regarding treatment of such morbid entity.

Objective:-

- To assess effect of intervention on low bone mineral density in thalassemia patients.
- To evaluate simplified protocol for management osteoporosis in multitransfused thalassemia major patients.

II. Material and Methods:-

❖ **Regular Blood Transfusion:**

The main criteria of an appropriate Blood Transfuion process are as follows.

1. Maintenance of red cell viability and function during storage, to ensure sufficient transport of oxygen.

2. Use of donor erythrocytes with a normal recovery and half life in the recipient.
3. Achievement of appropriate hemoglobin level.
4. Avoidance of adverse reactions, including transmission of infectious agents.
5. For deciding when to initiate regular transfusion regimen and whom to transfuse, the following should be considered:-

a. Confirmed laboratory diagnosis of thalassemia major
b. Laboratory criteria: Hemoglobin 2 weeks apart
c. Laboratory and clinical criteria, including Hb >7 g/dL with

- Facial changes
- Poor growth
- Fractures
- Extramedullary hematopoiesis

❖ **Chelation:-**

Cumulative iron burden is an inevitable consequence in TDT with 200 mg of iron accumulating for each unit of blood transfused.28 By the end of third decade, thalassemia major patient accumulates 70 grams of iron.24 Iron leads to multi-organ dysfunction with the liver, heart and endocrine organs being the most affected.

❖ **Innovative therapies in Indian context:-** Use of wheat grass therapy: wheat grass have potential to increase the hemoglobin levels, increase the interval between blood transfusions and decrease the amount of total blood transfused in patients with thalassemia major.Efficacy is yet to be established.

❖ **Use of hydroxyurea: -** It can cause induction of fetal hemoglobin and reduce ineffective erythropoiesis, and therefore, decreased symptoms in thalassemia intermedia patients.

❖ **Bone marrow hematopoetic stem cell transplantation (BMT):-** the only option for cure for homozygous thalassemia is to transplant healthy stem cells from an HLA-identical donor who is normal or heterozygous for thalassemia, which is capable of producing and maintaining a normal hemoglobin level in the recipient. This procedure is known as hematopoetic stem cell transplantation (HSCT).

❖ **Gene therapy: -** Availability of allogenic bone marrow is limited due to the inability to find an identical HLA matched bone marrow donor. Patients with severe thalassemia might benefit from new genetic and cellular approaches. Thalassemias are good candidate diseases for genetically based therapies in autologous hematopoetic stem cells. Alternatively, somatic cells reprogrammed to induce pluripotent stem cells might also provide a possible novel approach to treat thalassemia.34-35 The aim is to achieve a erythroid specific, position independent and stable gene transfer

III. Observation and Results:-

❖ I. Total number of participants in study were 42 (n=42).

II. Distribution of patients according to Dexa scan report:- Amont the participants, 19 patients had DEXA scan report between - 1 to -2.5 considering osteopenic. Rest 23 patient had DEXA scan report less than -2.5 being osteoporotic.

IV. Effect of no. of tranfusions on BMD before and after interventions.:- Mean numbers of transfusions receieved by patient was 198.43, Range 64 to 599 (SD = 96.3).

V. Effect of Pre transfusion hemoglobin level on change of BMD due to interventions:- Mean pre transfusion Hb level of the patients enrolled in study was 9.62 ; Range 7.1 to 12.1 (SD = 1.29).

VI. Effect of TSH on BMD before and after interventions:- Mean S. TSH level of the patients was 2.37; Range 0.21 to 7.24 (SD = 1.42). Only 4.76% of the enrolled study subjects (n=2) had high TSH level, being hypothyroid. Rest 92.86%patients (n=2) were euthyroid and 2.3% patients (n=1) had subclinical hyper thyroidism.

VII. Effect of S. ferritin level on change of BMD after interventions:- Mean S. ferritin level of the patients was 5460 ; Range 1091 to 11885 (SD = 2581).

VIII. Distribution of patients according to height:- Mean height of patient was 133.8 cm, Range 90 cm to 160 cm (SD = 16.23).

IX. Effect of stature on improvement of Bone Mineral Density:- effect of stature on change of BMD before and after intervention. (n=42)

Stature	No. Of Patient	Percentage	BMD befroe intervention	BMD after intervention	Difference of BMD
</= 130cm	15	35.7	-2.7	-2	-0.72
>130cm	27	64.2	-3.13	-2.16	-0.9

X. Effect of S. Estradiol on change in BMD Due to intervention. Mean S. Estradiol level of the patients was 40.23; Range 10 to 99 (SD = 27.09).Out of 23 female participants, 95.65% patients (n=22) had normal S. estrogen level. Only 1 patient (4.35%) had low S. estradiol level.
XI. Effect of S. Testosterone on change in BMD due to intervention. Mean S. Testosterone level of the patients was 1.18; Range 0.13 to 4.6 (SD = 1.53).In our study, among 19 male only 3 patients (15.79%) had S. testosterone value within normal range. Rest 16 patients (84.21%) had low S. Testosterone value considered to be suffering from hypogonadism.
XI. Effect of S.Calcium on change in BMD due to intervention. Mean S. Calcium level of the patients was 10.66 ; Range 7.9 to 13.2 (SD = 1.47). Among the enrolled patients, higher percentage of patient had higher calcium level. 16 patients have normal calcium level.
X Effect of S.Phosphate on BMD due to interventions. Mean S. Phosphate level of the patients was 7.07 ; Range 4.1 to 16.4 (SD = 3.16). Among the enrolled patients, most of the patients(92.86%) had higher phosphate level. Only 3 patients(7.14%) had normal phosphate level. None of them had low phosphate level.
XII. Effect of S. Alkaline Phosphatase on BMD after interventions. Mean S. Alkaline Phosphatase level of the patients was 132.3 ; Range 58.4 to 405 (SD = 69.73). Among the enrolled patients, higher percentage(59.52%) of the patients had low alkaline phosphatase level. 14 patients(33.33%) had normal alkaline phosphatase level. 3 patients(7.14%) had high alkaline phosphatase level.
XIII. Demographic Characteristic of patients:
XIIIa. Age wise distribution of patients: Mean age of patient was 14.14 years , Range : 8 to 20 years (SD=3.09 years).
XIIIb. Distribution of patients according to gender: Among the study group, there is slight female predominance male being 19, female being 23 , male to female ratio was 0.826.
XIV. Distribution of patients according to age at diagnosis Mean age of diagnosis of having thalassemia syndrome was 16.48 month , Range 1.5 months to 84 months (SD = 20.4).
XV. Distribution of patients according to weight Mean weight of patient was 29.27 Kg, Range 17 Kg to 48 Kg (SD = 8.1).
XVI. Spleen size: Mean spleen size of patient was 7.45 cm, Range 4 cm to 12 cm (SD = 1.96).
XVII. Liver size: Mean liver size of patient was 4.57 cm, Range 2 cm to 8 cm (SD = 1.59).
XVIII. Effect of SGPT on BMD due to interventions. Mean SGPT level of the patients was 60.4 ; Range 19.8 to 126 (SD = 25.79). Among the participants, only 26.19% of the patients (n=11) had normal SGPT value, rest 73.81% patients (n=31) had high SGPT value. None of them had low SGPT value.
XX. Effect of S. LH on BMD before and after interventions. Mean S. LH level of the patients was 1.4; Range 0.09 to 4.87 (SD = 1.50).Only 1 patient (2.38%) found to had high S. LH. and 16 patients (42.86%) had low S. LH where as rest 23 patient (54.76%) had normal S. LH level.
XXI. Effect of S. FSH on change in BMD due to intervention. Mean S. FSH level of the patients was 1.83; Range 0.05 to 6.03 (SD = 1.72).Majority of patients (76.19%, n=32) had normal S. FSH level. Rest 10 patients (23.81%) had normal level of FSH. None of them had high FSH level.
XXII. Effect of S. Progesterone on BMD. Mean S. Progesterone level of the patients was 0.24; Range 0.1 to 1.2 (SD = 0.25).In our study, out of 23 patients, 15 patients (65.22%) had low S. Progesterone whereas rest 8 patients (34.78%) had normal level.

IV. Conclusion:-

To conclude, our study "Assessment of bone mineral density in multitransfused thalassemia patients after intervention in a tertiary care hospital – interventional study " reveal, Osteoporosis is major cause of mortality in thalassemia major patients and is a progressive multifactorial disease.Although most of patients were asymptomatic in studied age group, evaluated early by measuring bone mineral density by DEXA SCAN. In our study these patients with low bone mass are treated with alendronate, calcium and vitamin D shows significant improvement in BMD after treatment. ($p =<0.01$).

Other factors like inadequate chelation, irregular transfusion, short stature, hypothyroidism, hypogonadism in thalassemia patients associated with osteoporosis were also seems to interfere with outcome of the management.

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