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BETA - THALASSEMIA: A CONVENTIONAL APPROACH

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ABSTRACT

Thalassemia syndrome is one of the most serious and common genetic conditions. In a large but unique geographical area, they are indigenous. Nevertheless, they disperse across areas that have not been affected before. Beta-thalassemia is caused by β globin genes mutations and is typically autosomal recessively inherited that contributes to beta-thalassemia results in imbalanced growth and erythropoiesis, consecutively. The seriousness of the disease depends in large part on the degree of chain imbalance. In the worst case, survival depends on normal blood transfusions, which result in transfusional iron and secondary iron-toxicity damage. Even in the case of milder syndromes, vigorous monitoring and treatment is required. The long lasting and high quality of life requirements are not recognized under measures such as the Global Burden of Disease project which ranks thalassemia in terms of years of life adjusting for people with disabilities (DALYs) very low and does not consider that it is high in the age group aged one to four years, thereby contributing significantly to mortality under the age of five. However, extreme cases of thalassemia are observed in most neonatal cell disease screening systems based on the screening technique. It is extremely useful because: (1) preparing the families affected for the illness of a baby is important and (2) secondary preventive measures.

INTRODUCTION

Epidemiology: Thalassemia is a genetically inherited disease resulting in deficient haemoglobin (Hb) development. It was historically widespread in tropical and subtropical parts of the world but now widely present worldwide. It is emerging as a global security threat [1]. Previously, only 35 thousand children were born with thalassemia per year, but now they have crossed 3-4 lakh per year. Nearly 80% of Thalassemic babies are born in low-and middle-income countries such as India, Bangladesh [2]. In India, high disease

burdens have been reported in some populations, such as Sindhis, Kutchhi, Bhanushalis, and Panjabis, from the western and northern regions with a disease burden of over 15% [3] while they are less frequent in South [4]. In few nations, also within the same geographic area, the distribution pattern is highly heterogeneousfor haemoglobinopathes [5].

DIAGNOSIS: Most people have been diagnosed with thalassemia within two years or at birth [Papageorgiou et al 2012].

PRENATAL DIAGNOSIS: If the doctor suspects, possibility that the fetus will be affected by this hereditary disease. The most common prenatal diagnostic methods available are Chorionic villus sampling (11^{th} week in which the placenta sample is taken) and Amniocentesis (16^{th}week in which the fetal fluid sample is taken) [6] and Cordocentesis (the cardiac puncture or hepatic vein sample is collected in the mid-trimester of pregnancy at 18-20 weeks of gestation) [7].

CLINICAL DIAGNOSIS: Generally, thalassemia major (TM) is diagnosed at early 2 years of age. Children reported severe microcytic anaemia, mild jaundice and hepatosplenomegaly. While intermediate thalassemia [TI] is suspected at a later stage of life with generally mild clinical manifestations. Carriers are usually asymptomatic, but show mild anaemia [8]

HAEMATOLOGICAL DIAGNOSIS:TM is defined as reduced Hb (<7 g / dL), mean corpuscular volume (MCV) is 50-70 and mean corpuscular Hb (MCH) is12-20 pg [7]. In TI, the Hb level is between 7-10 g / dL, the MCH level is between 16-24 pg, while the MCV in the blood is reduced to 50-80 fl. Thalassemia minor (Tm) is characterized by a low level of MCV and MCH of 62.8 and 20.7, respectively, but a significant increase in HbA_2 [9,10]. In these types, a high level of HbF in the blood will result in moderate to severe anemia usually between 3-12 months of age and confirmed at 1 year of age [7].

Peripheral Blood Smear Test: The RBCs include structural modifications microcytosis, hypochromia, aniseotic cell disorder, poikilocytosis and sideroblasts that are present in the individuals affected are put under a microscope. The count of nucleated cells significantly increased in relation to level of anaemia mostly after splenectomy. Carriers or Tm are less vulnerable than the person affected to systemic shifts in RBC. [8]

Qualitative And Quantitative Hb Analysis: These days analytical techniques such as HPLC, cellulose acetate, DE-52 micro chromatography is widely used, determines the amount and type of Hb present in blood both qualitatively and quantitatively.
$Beta^0$ thalassemia: Homozygote HbA is not present but HbF accounts 92-95% in blood.

$Beta^+$ thalassemia: Homozygotes HbA is between10 and 30% while HbF is between 70-90%.[8]

Genetic method: The phenotypic –gene-genotypic composition of the individual is chosen to be used in molecular tests for pathogenic variants or a single gene which is responsible for detecting the transition, for prediction of disease seriousness. Using the polymerase chain reaction, reverse dot blot analysis and prime-specific amplification with a complementary set of sensors or primers are typically identified by generally formed HBB mutations. If the PCR approach can not yield any results, sequence analysis is favoured.[8]

If the hematologic analysis shows abnormal, then molecular genetic testing of beta globin gene is performed torelate the reason of mutation [11]

Other Diagnostic Methods are:

CELL FREE FETAL DNA (cffDNA) IN MATERNAL CIRCULATION: Many experiments show that circulating nucleic acid [CNA] also serves as a diagnostic marker in patients with β-thalassemia. During fetal and placenta development in which non-cellular DNA constitutes 10 per cent of the overall DNA that can be observed at week 5 of pregnancy and rises over pregnancy, CNA rates are very small. CffDNA amplification is possible by various techniques, including real-time polymerase [PCR], nested PCR and massarray, digital PCR, next-generated

sequences or massively parallel sequencing. [12].

IRON TESTING: It tests the quantity of iron in the body. This includes an unsaturated iron binding capacity (UIBC), complete iron binding capacity (TIBC) and transferrin saturation per cent in order to assess whether or not iron deficiency is related to sickness [13].

Heterogenicity of Haemoglobin (Hb):

Hb is a tetramer composed of 2 alpha (α) and 2 non α (usually β, γ or δ) globin chains. Hb is a tetramer.A single molecule of Fe^{2+} Protoporphyrin IX is used for growing globin of polypeptide. Every tetramer has about 64,000 molecular weights and each α- and β-chain has about 15,750 and 16,500 molecular weights [15] respectively. Haemoglobin main function is to transport oxygen andcarbon dioxide into and out of the body's circulatory system. Different anemia forms may lead to HB deficiency, e.g. anemia with iron deficiency, hemolytic anemia. Globin chains of Hb combine in varying fashion accounting for different type of Hb[Angastiniotis et al] :

Alpha chain combines with beta chain to form adult Hb (HbA_1) represented as ($\alpha_2\beta_2$), which accounts for 95 % of total Hb.

Alpha chain combines with delta chain to form minor fraction of adult Hb (HbA_2) represented as ($\alpha_2\delta_2$), constituting less than 3.5% of total Hb.

Alpha chain combines with the gamma chain into a fetal Hb (HbF), which is (α2β2) and plays a significant role in the oxygen flow into tissues and organs. HbF is predominant at 1-2 month gestation stage, accounting for 80% and then turning to HbA which remains HbF up to 1%.[14,15].

Glycosylated Hb (HbA_{1C}): Used to differentiate between iron-deficiency anemia and thalassemia minor [26].

Heterogenicity of Thalassemia:

Thalassemia is defined as the decrease or ineffective production in the haemoglobin molecule of one of the polypeptide goblin chains, which results in multiple-gene interactions of the thalassemic phenotype. This mutation in the globin chain is founded and leads to faulty production of haemoglobin. Addition or replacement, rarely with a gross deletion of genes or immediate flank sequences can lead to molecular defects. However, in most cases, only one nucleotide substitution is responsible for mutation. [17]. Variant of gene activity and irregular Hb for the development of a wide spectrum of variable severity thalassemic disorders.

Major Thalassemia Beta: Thalassemia major individuals are typically diagnosed by age 2. The baby who comes with pale skin and has problems with feeding, diarrhoea and other complications which lead to development and growth retardation. The hemoglobin values should be 7-9 g / dl for maintenance and a daily transfusion protocol should be mandatory. Hypogonadism, hypothyroidism, diabetes and much more may be part of the complications of iron overload. [ref 15,16].

Moderate thalassemia: Patients are prone to mild anaemia because daily transfusion of blood is not required. They are able to survive but they are still less growth and development. They fear iron overload but they are not generally linked with hypogonadism, hypothyroidism, diabetes [18].

Thalassemia Minor: It's a heterosymptomatic disease and the patient has a haemoglobin mutation in the β-globin chain. In patients with homozygotic thalassemia, typically asymtomatic and 25% babies are at risk. They experience moderate anaemia occasionally. [8].

There were also other forms of thalassemia

Hb E-beta thalassemia: if the individual has one gene Hb E and one gene beta. The occurrence is seen in South East Asian and African origin contributing to relatively extreme thalassemia-similar anaemia intermediate, though carriers are 50% and widespread in the north-east states of Indians [27]. For screening carriers with hemoglobinopathies, the DCIP test (Di-Chlorophanol-Indo-Phenol) is used [7, 13]. Hb S-beta thalassemia: when a person with one gene Hb S and one gene beta thalassemia. This Hb variable thalassemia is the most common

type, as severity depends on the amount of beta globin produced [13, 19]. α globin chromosome at 16 incorporates two genes (HBA1 and HBA2) while beta-globin cluster on its chromosome 11. In the case of diseases, the physiological state is disrupted by the equilibrium in which α and non-α globin development can not guarantee a matched pair in the standard tetramer. More work is required to estimate the actual burden of disease (HBA gene version) and the capacity to generate α-chains (HBG_2 gene modulator) that bind to the available fetal formation (HBF).The poor processing of one of the globin chains within RBC growth would lead to a selection of the globin chain that is usually produced and cannot produce heterotetramers in comparable quantities. In the erythroid precursor of the mature RBC and bone marrow the precipitated unbonded chain was obtained which may result in haemolysis and ineffective erythropoiesis [20]. If beta chain building up, it leads to α thalassemia (contributes 20 percent) and precipitation of α globin forms beta thalassemia (Contributes 5.2 percent) [21]. The other consideration is the rise in the number of inbred marriages in low- and middle-income countries that contribute to high prevalence recessive genetic trait strain even though the exact knowledge on inbred marriages does not exist. The longevity is increased by early intervention and better treatment as they now survive longer .Homozygote HBB beta thalassemia mutation either develop Thalassemia Major where chronic blood transfusion is commonly used for medical purposes only and Thalassemia intermediate and do not require daily transfusion with moderate anaemia. [22].

Therapy and Treatment:

TRANSFUSION DEPENDENT THERAPY (TDT): Earlier there is only blood transfusion therapy and iron chelator drugs being consider to be prime therapy for the management for TM and TI that can only provide symptomatic relief and prolongation of disease or symptom availing livelihood to patient. But itself associated with many other complications like renal impairment, cardiac complication etc. Therefore, need of meticulous therapy in order to reduce complications [23].

BLOOD TRANSFUSION: This helps to alleviates week symptomatic anaemia, to remove inadequate erythropoiesis, to boost growth and development, to minimize the excess of iron from improved gastro-intestine absorption and to prolong life. This therapeutic choice is also focused on the clinical characteristics of patient associations with genotype-phenotypes. Each third of the week transfusions are held at a rate of 9-11 Hb transfusion. Packaged red blood cells (PRBCs) are chosen for the purpose of reducing febrile non-hemological transfusion reactions and decreasing the risk of infection and alloimmunism from cytomegalovirus. In most patients with thalassemia, transfusion can lead to an overload of iron with an implication of 90 percent death as well as increased absorption of iron through the gastrointestinal (GI) tract[24]. When thalassemia major patients receive regular blood transfusion, iron overload become unavoidable because the human body lacks a mechanism to excrete an excess iron. Thus, amongst them blood transfusion is a key of overload as it may leads to heart failure, cirrhosis, liver cancer, growth retardation and multiple endocrine abnormalities. Thus, main challenge of iron chelating agents is to balance accumulation of iron in body. Currently these agents are clinically used [16]. *Desferrioxamine (*DFO): An hexadentate which binds with iron 1:1 fashion [25]. Because of its short t1/2 it is administered continuously with the help of infusion pump subcutaneously for 12–14 h daily. But peripheral field defects and sensori-neural hearing loss occur when given for longer time. It should be given at age of 2 yr if ferritin levels is maintained between 1000 and 1500 ng/ml. It is given at a dose of 30–50 mg/kg/day [28]. An observational study, involving 977 patients with TDT, demonstates the efficacy and survival benefit for DFO in patients. The rate of survival was increased progressively [24].

Deferiprone (DFP): Invented by Hider's laboratory. It is more effective than DFO in deploying iron from the heart. It is given at a dose of 70 - 100 mg/kg/day that is 2-3 times a day as it binds in 3:1 fashion[25].Among which 20% of children with high serum ferritin level develop arthropathy and less than 1% develop severe neutropenia [4]. In was approved in

Europe in 2009 when the DFO gets contraindicated in Transfusion dependent thalassemia. In 2011, USA granted permission to used deferiprone in treatment of transfusion iron overload [29,30].

Deferasirox: A tridentates which binds in 1:2 fashions as well. It is twice as effective as DFO. It mainly acts iron from reticulo-endothelial cells, parenchymal cells of various organs and also inhibits myocardial cell iron uptake and removes iron directly from the myocardial cells. It is given at a dose of 30 – 40 mg/kg/day.There is no arthralgia, cardiac, ocular or vestibular side-effects. It is now considered as a gold standard chelating agent [28, 31]. Body iron levels can be measured by methods like serum ferritin, biopsy, SQUID & MRI T2 etc. Among these tests MRI T*2 is more common and provides liver and cardiac iron overload more precisely.But these days combinational therapy used as more accurate management of iron level will be used which is not achieve by one drug as it accessible to different iron pools,prevention of non-transferrin bound iron accumulation with better compliance and good HRQoL(health related quality of life)[4]. Another challenge is for adhering to regimens throughout a lifetime, as even small interruption to treatment can have damaging effects.

Complications:

CARDIOVASCULAR DISSEASE: *In-vivo* model of mice shows that accumulation of iron reported at 12 month of age of mice [32]. The accumulation of iron is leading cause of mortality and morbidity (63.6% to 71%)in diseased patients.It is due to evidence of lipid peroxidation via the Fenton-catalyzed Haber-Weiss reactionleads to formation of toxic hydroxyl radicals responsible for cardiomyopathy [33].Some of the symptoms are associated with the prevalence of 6 and 4% respectively, such as coronary attack, heart failure, arrhythmia, and thromboembolic cases [34].

LIVER DISEASE: Liver disease is another common cause of death in transfusion-dependent thalassaemia patients. Hepatic iron overload is associated with increase in blood transfusion [35] and dyserythropoiesis [36]. Anaemia and hypoxia also responsible in iron overload by decreasing the impact of erythropoietin on hepcidin synthesis. The diagnoses of complication are based on clinical and related parameters through which we regulate or manage the complication in realtion to beta thalassemia [37].

ENDROCRINE COMPLICATION*:* The iron deficiency of the drums ultimately results in hypogonadism, hypoprolactinaemia, decreased re-serves of ACTH, elevated cortisol levels and hypoparathyroidism [38].Prior monitoring of gonadotropins (LH and FSH), testosterone in males, and estradiol in females are some useful bio-markers, helpful for early evaluation of hypogonadism [39], it may leads in osteoporosis and infertility risk in future [40].

PAIN: Despite of the continual improvement in therapies, thalassemic patient whether transfusion or non-transfusion are increasing recorded pain. There are many tools available to access the frequency and severity of pain such as Child Health Questionnaire (CHQ PF-28), and the Medical Outcome Study Short Form-36 (SF-36) and Hospital Anxiety and Depression Scale (HADS), but no exact result it observed [39]. The incidence of pain is correlated with age as patient ages, prominency of pain is expands [41]. According to the study conducted Trachtenberg et al 69% of adults/ adolescent observed moderate pain in 28% through SF-36v2 health survey while 56% of children in which only 11% explicit pain through PF-28 child health questionnaire [42].

NEURAL COMPLICATION: As we know that in homozygous state,TM causes severe, transfusion dependent anemia while in heterozygous state, the Thalassemia trait (i.e., thalassemia minor) causes mild to moderate microcytic anaemia [43]. Many of the studies observed central and peripheral neural complication like intellectual impairment and mental retardation has observed for being in mutual relationship with each other [44, 45]. It is due to iron deposition in putamen, caudate nucleus, and motor and temporal cortex of brain is of paramount for cognitive function and clear memory [45, 46].

INFECTION: Iron overloading may also lead to mortality in which infected related death might occur. Iron chelation leads to decrease innate immunity associated in reduce level of T-cell, B-cell, immunoglobulin and neutrophils level in body [47], which is responsible microorganisms such as human parvovirus, human immunodeficiency virus (HIV), human cytomegalovirus (HCMV), yersinia enterocolitica and other species could easily attack on body [16].

OCCULAR COMPLICATION: Patient suffering from beta thalassemia is being recognized as diverse ocular and systematic complication. Complication includes decreased visual acuity, colour vision anomalies and nyctalopia, to visual field defects, cataract, retinopathy and optic neuropathy in which many of them is caused by using desferrioxamine and deferriprone [48]. Taneja et al conducted an study in which patient are divided in 4 groups. Group A received only blood transfusions, Group D blood transfusions with deferriprone Group B blood transfusions with desferrioxamine subcutaneously, Group C blood transfusions with desferrioxamine and oral deferriprone, Lenticular opacities (44%) and visual acuity (33%) is recorded [55]. Deferoxamine is most likely to cause change in scotopic retinal [49].

RENAL COMPLICATION: The renal abnormalities are most likely cause byiron chelators in transfusion dependent beta thalassemia [50] consider to be 4th major complication among other [51]. These abnormalities are decrease in glomerular filtration rate [56], tubular dysfunction [52], haematuria [53] and nephrolithiasis [54]. A retrospective studies demonstrate that deferasirox on long term use reduces iron overload in hemodialysis patients, likely due to increase iron metabolism in them [31] while other drugdesferioxamine shows that tubular dysfuction [52]. Demosthenous et al had conducted a narrative review that eplicit the occurance of neural complication associated with iron chelators [57].

Drugs for Treatment and Management:

FetalHemoglobin (Hb F) Inducing Agent: A pharmacologic agent improves HbF, a gamma globin synthesis that increases alpha-beta globin imbalances that increase the life span, decreases inadequate erythropodesis and hemolysis, thus decreasing beta thalassemia mortality. Few other compounds, such as demethylated inductors of HbF, histone deacetsis (HDAC), and hydroxyurea, are also involved in the same way.

Demethylating Agents (5-azacytidine and decitabine): It is a cytidine nucleoside analog that is integrated into DNA where DNA (DNMT) is removed and DNA hypomethylation is caused, which eventually leads to a gamma globin expression. Some experiments have also been shown to increase the Hb level. Bad effects include mutagenicity, myelosuppression [58]. In contrast with 5-Azacytidine, decitabine (5-az-2′-deoxycytidine), an azacytidine analog is considered free as it earlier approved children with acute leukemias [58, 59, 60]. A pilot study was observed that decitabine is well tolerated with pleasing red blood cell indices changes recorded when 0.2 mg/kg is given twice per week for 12 weeks shows remarkable increase in Hb level of 1 g/dl [61].

Histone Deacetylase (HDAC) Inhibitors: Butyrates and short chain derivatives of fatty acids contribute to an HDAC inhibition that enhances the acetylation of the central histone, changes the chromatin structure, and thereby decreases the gene transcription rate.Infants born to mothers with diabetes had high butyrate levels and a delayed fetal switch to adult hemoglobin is evident [62]. Thus, stimulates HbF development as well as the release of alpha globin and minimizes the excess in the globin chain. This epigenetic modifier down regulates the expression impedes enzymatic machine responsible to keep chromatin structure in its form [63].

Erythropoietin: It is a hormone produced primarily by the kidneys which plays a key role in the production of red blood cells (RBCs) that shown to increase total HbF level in TI but not in case of TM. It has a potential of using along with hydroxyurea in patients with low erythropoietin levels [64].A study in which 58

patients of TI involving 35 men and 23 women are selected. The dose of 10000 IU subcutaneously is given for about 6 months to check its efficacy in TI. More than 50%, 55 patients shows increase in Hb level while only few of them, 3 patients not responded at all [65]. In other study involving 12 Tm patients whether chronic erythropoietin is effective or not. Treatment are planned for one year and additional one year for maintenance, shows increase in Hb level without use of blood transfusion [66]. One studies states that it act as an antioxidant for RBC and platelets which might results in anemia and thromboembolic complications in these patients [67].

HYDROXYUREA: It was earlier approved in the treatment of sickle cell anaemia and now it used to compensate the requirement of blood transfusion [68, 70]. Some of the studies responded to beneficial although other shows no as such results [69].Hydroxyurea is a ribonucleotide reductase inhibitor that has potential to induce Hb F production in thalassaemic patients. Hydroxyurea is given at a dose of 8–10 mg/kg/day initially and escalated to tolerated limit upto 20 mg/kg/day [71]. Nonetheless, treatment with hydroxyurea was closely monitored because of its adverse effect [70] . However, an interventional study was conducted to test the hypothesis whether drug correct the anemia in patients with TM or not [72].

SPLENECTOMY: Splenomegaly may cause extramedullary haematopoiesis. Due to exacerbation of chronic haemolysis cause worsening the anaemia and increasing transfusion requirement in patients. The risk of doing splenectomy results in post-splenectomy sepsis, multiple studies have highlighted an increased risk of other post-splenectomy complications in thalassemia, including pulmonary hypertension, heart failure, thrombosis, cholelithiasis, leg ulcers, osteoporosis, brain infarcts, and others. Therefore, splenectomy should be avoided unless absolutely indicated or if thereare clinically significant complications such as pancytopenia and marked enlargement of spleen [73]. Doctors recommended to decrease the requirement of transfusion and augment Hb level among the patients of TM. But it was only utilized when more than 200-220 mL RBCs/kg/y with a hematocrit value of 70% [74]. Thereby not meant to permanent alternative from transfusion While splenectomy might occur in TM but in the patients of Tm cholecystectomy is preferred as the results shows no statistical difference in prevalence of gall stone [75].

Activin receptor ligand trap:

Sotatercept which comes under ACE inhibitor class is an Activin IIA Ligand trap. It works on erythroblast by doing differentiation at its terminal site as it gives astonishing results in preclinical period. It may also act through other ways by lowering the unstable alpha gobin level and consequently improves its structural morphology. Ultimately it increases the Hb level while being used for osteoporosis [76]. (NCT01571635) In a phase II clinical study shows that sotatercept blocks erythropoiesis in its late phase in transforming growth factor. This study tooks more than 22 month in order to check the safety and tolerability in adults with beta(b)-thalassemia [77].

Luspatercept: Which Activin IIB Ligand rather than IIA that is recently in phase 3 in England and is already being approved by US-FDA 2019 for the treatment of anaemia in adult patients with beta thalassemia who require regular red blood cell transfusions. It significantly improves maturation of erythroid and hereby decrease the transfusion burden in transfusion dependent thalassemic patients and decrease liver iron level. In a Phase III BELIEVE trial shows increase in reduce transfusion burden in patients of thalassemia [78].

Ruxolitinib: It plays an important role in lowering the size of spleen for short time period in pre-clinical study [79] which is even confirmed in phase II study of ruxolitinib to demonstrate effectiveness in transfused patients [80]. And because of this reason it is used in TM and occasionally in Tm. It is a JAK2 inhibitor that shows good improvement in Hb and due to this it considered to be a good alternative to splenectomy in patients with hypersplenism. [23].

HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT): It is anautologous haematopoietic stem cells (HSC) obtained from the patient's own bone marrow (BM) or peripheral blood (PBSC) or allogeneic HSC where the donor cells (family-related or an unrelated), from the bone marrow, peripheral blood or cord blood. Previously it considers to be only potential cure of disease as it having remarkable success rate but patients with high risk are having more chances of graft rejection, infection from staphylococcus, aspergillus species and many more after HSCT transplant-related mortality [81]. HSCT is count on to be most acceptable a curative treatment resulting in a long-term quality of life as that of the general population [82].

BONE MARROW TRANSPLANTATION: Edward Donnall Thomas was stared for first successful bone marrow transplantation in 18-month-old child using an HLA matched elder sister as the donor and miraculously the child was cured. There are various principle associated with the use of this therapy:

- Destroy and prevent regeneration of defective stem cells.
- Sufficient immune suppression for good engraftment.
- To infuse stem cells with the normal gene.
- to prevent Graft versus host disease (GVHD) with proper combination of immunosuppression and infection management. [4]

NON- TRANSFUSION DEPENDENT THERAPY (NTDT): It is defined as a sub-type of inherited haemoglobin disorders in which orderly intake of blood transfusion for prolong period is not essential although occasional intake is preferred in certain conditions like splenomegaly, pregnancy and others. It includes β-thalassemia intermedia, hemoglobin E (HbE) β-thalassemia, and hemoglobin H disease [83]. The NTDT can be caused by milder variant of beta Globin mutation which is inherited to provide sufficiently globin gene of some adult haemoglobin production in interstitial diseases [84] to promote appropriate safety, growth and development. Another factor responsible for the decreased thalassemia severity is the co-heritance of α thalasaemia, or the disposition of a genetic determinant of enhanced fetal haemoglobin output [85]. When there is absence of transfusion therapy, abundance of underlying proceeds in ineffective erythropoiesis and peripheral hemolysis leads to various unsympathetic complication in patients of NTDT and these complication are comparably even higher than transfusion-dependent patients [86]. Progressive iron overload results due to down-regulation of hepcidin causes increased intestinal iron absorption and escalate release of reused iron from the reticuloendothelial system [32, 87].

TREATMENT STRATEGY:

TRANSFUSION: As a consequence of infection, pregnancy, surgery, accelerated growth and puberty, pregnancyrequires occasional transfusion where chances of acute blood loss is observed [88, 89]. In red cell alloimmunization, phennotype matching is essential as it is recommended more frequently. However, older patients can quickly become symptomatic of anaemia and should be prescribed for the daily transfusion system [89]. It is to choose best mordality after detecting the disease and before we utilize any therapy particularly transfusion therapy, too quickly. Patients even on small infection has to undergoes unnecessary treatment if those having low Hb level [90]. However, in few patients where transfusion become necessary for maintainance of normal activity, growth and development and to prevent skeletal deformities [91]. But RBC transfusion therapy is even leads intensifies iron overload and cardiac dysfunction but these condition minimize with proper phenotypic blood matching in pregnancy [91, 92].

SPLENECTOMY: liver fibrosis, thrombocytopenia, vomiting or symptomatic anaemia are the main causes of hypersplenism [93]. The large number of clinical symptoms was also often observed. In order to increase Hb, Splenectomy was often considered in NTDT. But his treatment is also accompanied by risk of severe infections, life-threatening post-splenectomy sepsis. So prior to initiation of therapy patient is allowed to vaccinated

before 2 month with pneumococcal vaccine, Haemophilus influenzae vaccine, and the meningococcal vaccine [94]. As after surgical removal of spleen incidence of thromboembolism, Endocrine and bone disease, leg ulcer, predispose to pulmonary hypertension was spotted [91].

CHELATING AGENTS: There are various drugs and similarly numerous uncontrolled trials of chelation therapy DFO, DFP to demonstrate its safety profile in NTDT. But only deferasirox which is actually approved for NTDT by both FDA and EMA based study published in the THALASSA trial [70]. When the cut-off LIC value of >5 mg/g dw results in proportionate increase in the risk of NTDT patients PHT, hypothyroidism, hypogonadism, osteoporosis and thrombosis [95, 96] as LIC of >5 mg/g dw correlated with a serum ferritin of >800 ng/mL, signifies to begin the use of chelation therapy [97].

HYDROXYCARBAMIDE/ HYDROXYUREA:

Hydroxyurea is a cytotoxic agent which acts by restraining intra- and extramedullary erythropoietic activity and improves fetal haemoglobin production [96]. This drug reduces anaemic symptoms, jaundice, bone marrow and spleen enlargement, mitigation of bone pain and retrogression of extramedullary masses which leads to reduce transfusion requirement [99]. An OPTIMAL CARE study shows decrease in extramedullary hematopoiesis, osteoporosis, leg ulcers, hypothyroidism, and PHT was observed when the patient is on hydroxyurea therapy [98]. While another studies elucidates 6 months of therapy will gives remarkable increase in Hb concentration in blood with few conditions like rashes, alopecia, gastrointestinal disturbances, and myelotoxicity [96].

CONCLUSION:

Most of the cases of beta thalassemia is of severe conditions. This narrative review highlights disease epidemiology, its diagnosis, heterogeneity of Hb in relation to beta thalassemia and associated management mordalities. It became essential for precise detection of complication associated with iron chelators overload in NTDT and TDT patients as there life expectancy might get escalates but associated complication might deteriorates its clinical significance on its prolong usage. The regular surveillance followed by the early start of iron chelation therapy is necessary for better prognosis in cases. Controlled doses of chelating agents are also important for the normalicy of patho-physiological functions . The patient's quality of life must be strengthened by a multidisciplinary treatment plan that tackles their medical , dental, orthopedic and ophthalmic issues found in this research as the mortality rate has increased.

Conflict of interest: -Nil-

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