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Original Research Article

A SAFETY AND EFFICACY OF COMBINATION THERAPY OF DEFERASIROX AND DEFEROXAMINE VERSUS DEFERASIROX FOR TREATMENT OF TRANSFUSIONAL IRON OVERLOAD IN SICKLE CELL ANEMIA IN AL-NAJAF AND BABYLON PROVINCE IN IRAQ

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Abstract:-

Background :- In Sickle cell anemia , transfusions improve blood flow by reducing the proportion of red cells capable of forming sickle hemoglobin polymer .This limit hemolysis and endothelial damage and repeated blood transfusion leading to iron overload or transfusion hemosiderosis ,the only way to prevent this is by long-term chelation therapy. **Objectives: -** The aim of this study is to assess the efficacy and safety of combination therapy in a group of patients with sickle cell anemia. **Patients and method**:- The prospective study done on sixty five patients with the sickle cell anemia , conducted to Al-Najaf and Babylon thalassaemia centers ,classify into two group, those on combined therapy of Deferoxamine-Deferasirox treatment as second group , while on Deferasirox alone as first group and its aim to asses safety of combined treatment . **Results: -** Both regimens proved to have less adverse effect on hepatic or renal function and platelets count. The degree of reduction of serum ferritin is significantly higher with combined Deferoxamine-Deferasirox therapy. **Conclusion**: - combined chelating agents have significant effect on serum ferritin, with acceptable level of safety.

Key wards: Sickle cell anemia, Iron overload, Serum ferritin, combination therapy.

Introduction:

Sickle cell anemia (SCA) is an autosomal recessive genetic disorder caused by a single nucleotide mutation of the Hb β chain (substitution of valine for glutamic acid in the sixth position of the beta chain of the Hb molecule) together with the normal gene for adult Hb (HbA) result in a mutant protein giving rise to a defective variant of Hb [(1).]

Unlike people with β thalassaemia major , who require regular blood transfusion throughout life from soon after birth , the majority of people with SCA require red cell transfusion only occasionally and intermittently[.(1)].

The transfusions improve blood flow by reducing the proportion of red cells capable of forming sickle Hb polymer. This limit hemolysis and endothelial damage that

result from high proportions of sickle polymer containing red cell and also transfusions are used to increase blood oxygen carrying capacity in sickle cell patients with severe chronic anemia or with sever anemic episodes.[2]

However, with each unit of transfused blood, 200–250 mg of iron is transferred to the patient. There are no natural means of removing excess iron from the body and so iron gradually accumulates (over 5–10 years) to toxic levels that affect major organs such as the heart and liver[3]. nonetheless, patients with SCA are far less likely to be screened for end organ damage than patients with the thalassaemia despite a similar transfusion history.[2] (with repeated transfusions , serum transferrin becomes saturated and the excess circulating iron is transported as non transferrin bound iron (NTBI) which enter cell in a dysregulated fashion and a subset of NTBI called Labile Plasma Iron (LPI) , may cause end organ damage)[2].This condition, commonly known as iron overload or transfusion hemosiderosis. The only way to prevent this is by long-term chelation therapy.[4]

Recent evidence suggests that serial of iron concentration in steady state correlate significantly with liver iron concentration through magmatic resonant imaging (MRI) T2*. [2].

Liver iron content has been accepted as the most accurate quantitative means of determining whole-body iron concentration. However, liver biopsy is not indicated for routine assessment due to its invasive nature. [5].

Serum ferritin of > 1000ng / ml used as a guide in patients with thalassaemia, is not validated in sickle cell disease (SCD). while in SCD , the ferritin level of over 3000ng/ml are associated with hepatic iron concentration (HIC)of more than 10 mg/g , values between 1500 and 3000 ng/ml are not predictive of an elevated HIC [2] . A better parameter for invasive estimation is transfusional iron load (TIL), where TIL of more than 100 mg/kg has been closely correlated with high liver iron store and liver fibrosis in the pediatric population and is indicated to start chelation therapy [2].

Deferoxamine (DFO) has until now been considered the treatment of choice for patients with chronic iron overload. However, continuous parenteral administration makes DFO less attractive and compliance is poor [2].

The first oral iron chelator introduced to the US was Deferasirox (Exjade, NovartisPharma AG), which is additionally licensed in Europe and other regions for the treatment of iron overload. Its long half-life of 11–19 hours maintains plasma levels within the therapeutic range over 24-hour period, allowing for a convenient once-daily oral administration and offering a viable option over deferoxamine and its associated problems with compliance.[6]

Deferasirox is an orally active iron-chelating agent that binds iron in a 2:1 ratio and is primarily excreted in feces. It is given once daily as an oral suspension (usually in water or fruit juice) at a dose of 10–40 mg/kg. [7]

The ease of administration of Deferasirox (oral) compared with DFO (infusion) might improve patient adherence to therapy [7] and, if effective, may also improve quality and quantity of life. [8]

Aim of study:-

The aim is to assess the efficacy and safety of combined Deferoxamine-Deferasirox therapy for patients with sickle cell anemia.

Patients and Method:

The prospective comparative study was done on 65 patients with sickle cell anemia, their ages range from 3-15 years with mean 9±1.5 years, classified into 38 males and 27 females, with iron overload from repeated blood transfusions. The serum ferritin level for entry into screening period of this study was ≥ 1500µg/L, conducted in Al-Najaf and Babylon thalassemia centers from March 2013, until end of February 2014.

Thirty three were chosen to have deferasirox therapy as group one, starting oral dose 30mg/kg/day. Its protocol specified adjustment of 5 mg/kg/day based on 3 months serum ferritin and safety marker, till dose of 40 mg/kg/day , while Thirty two patients as group two were already on deferoxamine therapy on dose of 20-40 mg/kg/day ,subcutaneously infused by special portable device,12 hour a day, five days a week. when they were chosen to enter the study, their therapy changes to combined deferoxamine (DFO) 20-40mg\kg\day infusion two days per a week, and deferasirox (DFX) in dose of 40 mg\kg\day seven days a week (for those patients given initially 30mg/kg/day for 2 weeks to look for deferasirox tolerance and then increased dose immediately to 40 mg/kg/day if can tolerable). Hemoglobin levels of all patients were maintained between (8.6-9.8gm|dl).

Serum ferritin level on DFX was (3100-9600mcg/L), while ferritin level of those on combined therapy were (5268-9035mcg/L).

Monthly blood aspirate for cell blood Count (CBC), C-reactive protein(CRP) , ESR ,serum ferritin (we measure serum ferritin if clinically stable and no evidence of inflammation as negative C-RP , normal ESR and white blood cell count), alanine aminotransferase (ALT) , aspartate amino transferase (AST), blood urea, serum creatinine, urine examination for proteinuria, while visual, auditory examination and echocardiography were tested before and after treatment.

Patients were excluded if the serum creatinine above the upper limit of normal, alanine amino transferase above 300U/L or if they have systemic disease like cardiovascular , renal , bleeding tendency and active hepatitis B or C((active hepatitis B was defined as liver function tests above the normal range, together with a positive antigen (hepatitis B e antigen , hepatitis B surface antigen), while active hepatitis C was defined as liver function test above the normal range in a presence of a positive hepatitis C antibody test and detectable hepatitis C RNA levels).

All patients or parents provided oral informed consent before being allowed to enter the study.

Statistical analysis: - was performed by SPSS 16.0.2. Differences were considered significant at P value <0.05, highly significant of <0.01 and not significant if > 0.05.

Results:

One trial, involving 65 patients with SCA, the mean age is. 9± 1.5 years, 38 males 58.6% and 27 females 41.4%. The median base level of SF of combined therapy group 6337mcg/L (range 5268-9035 mcg/L), while the its median level on monotherapy 5500mcg/L (ranged 3100-9600 mcg/L), compared the efficacy and safety of combined therapy (deferasirox – desferioxamine) to monotherapy of deferasirox alone after 12 months of study.

The median level of SF seem to be decreased more effectively after 12 months of study (on combined therapy was from 6337 to 4857µg/L, while its level on monotherapy group was from 5500 to 4518 µg/L). SF was reduced in second group -1480µg/L, while -980µg/L in the first group.

Table 1:-shows median SF level decreased significantly in group one at the end of study one year later from base level was- 982µg/l with p-value is significant 0.0124

Table 2:-there was significant difference of SF level in group two at the end of study from the base -1480µg/l with p-value is 0.012.

There were no significant difference of renal function test, liver function test, platelets, visual, auditory and echocardiogram from base to the end of study in both groups of study.

Table one:-liver enzymes, renal function tests changes for patients on Deferasirox alone (first group)

Test	Range of base	Base –mean	Range of end	End - mean	P value
S F	3100-9600	5500	2500-8100	4518	0.012
B U*	24 – 35	30	23-50	36.4	NS
S. C*	60-130	88	70-146	108	NS
ALT*	25-100	45±20	35-120	50±25	NS
AST*	15-74	40±12	30-91	43±18	NS
Platelets	120-350	210	105-250	160	NS
Visual		normal		normal	
Auditory		normal		normal	
Echo		normal		normal	

Table two: variables over one year for patients on combined therapy (second group)

Test	Range of base	Base –mean	Range of end	End-mean	P value
S F	5268-9035	6337	4115-8114	4857	0.001
B U*	25-34	27.5	24-51	39.5	NS
S C*	70-135	90	75-155	120	NS
ALT*	30-104	44± 23	30-131	50± 21	NS
AST*	32- 90	40±11	29-109	42±13	NS
platelets	130-330	230	110-230	155	NS
Visual and auditory		normal		normal	
Echocardiogram		normal		normal	

Table three: Variable factors on both groups at the end of the study

SF (decreased level) mcg/l	Monotherapy group	Combined group	P value
Renal function test blood urea mg/l(mean) S. creatinine mg/l(mean)	-982	-1480	0.05
Liver function test SGPT U/L(mean) SGOT U/L(mean)	36.4 108	39.5 120	NS NS
platelets	50±25 43±18	50±21 42±13	NS NS
	160	155	NS
Visual and auditory	normal	normal	
Echocardiogram	normal	normal	

Normal ranges:-*
Blood urea (BU): 20-40 mg/ml, serum Creatinine: 62-124 Mmol/L
SGPT: 10-45 U/L, SGOT: 10-45 U/L , platelets count: 150-300

Discussion:-

Sickle cell disease results in acute complication and progressive multi-organ failure. Transfusion therapy reduces the number of erythrocytes containing sickle HB and reduce vascular complications associated with the disease.[9]

Results of this study show serum ferritin were decreased significantly in both groups but it was more effectively in the second group .(Its level was reduced - 982µg/L in first group, while in second group combined therapy was decreased- 1480µg/L) with p-value 0.05. although ,the use of falling ferritin as a guide to dose reduction can be unreliable in SCD as the SF can be raised for several weeks after a vasocclusive event independently of iron loading [10]. However, we are measured SF in the study during stabilizing condition with no crises or no evidence of inflammation.

Deferasirox is effective oral iron chelator with a long half-life, which could be used as monotherapy. It could provide constant gap-free chelation coverage with a single daily dose, and efficient and selective role on organs such as endocrine gland and liver. [11] However, its efficacy on the high iron overload is questionable. It could not achieve a negative iron balance even with highest recommended dose.

The iron chelator Deferoxamine is recommended for patients with iron overload in SCD, when used appropriately, it effectively reduces iron burden, however, due to short half life and poor oral bioavailability, it must be given subcutaneously or intravenously, usually over a period of 8-12 hours for 5-7 days / week [10]

Such regimens are extremely burdensome and often lead to poor compliance, particularly in adolescent patients [12] those who do not comply with their treatment are usually undergo chelation in-adequately, which has a significant impact on survival. This is especially a concern for iron-overloaded pediatric patients because most will require lifelong chelation therapy [13]. So, none of iron chelator drugs could provide all therapeutic goals.

Medicines with different properties and mechanisms may access different iron pools, different dosing schemes or a combination of deferasirox with other iron chelators should be performed to establish the optimal treatment algorithm for individual patients based on their iron overload status. [2] .The molecule of Deferasirox is small and can easily enter into cells and is able to transfer iron into plasma for DFO. [14]

Combined DFO (20 mg/kg/day, 2days/wk.) and DFX therapy (40 mg/kg/day, 7 days per week) have shown significant and safe decline in mean serum ferritin (6337 mcg\l to 4850mcg\l) with no clear changes in hepatic or renal function. [11]

Combined regimen was associated with minimal adverse effect as it was showed by insignificant changes in liver enzymes, BU, serum creatinine and platelets count, also has no significant changes in assessment of vision, hearing and echocardiogram at the end of study in comparison to the beginning of therapy.

The commonest side effect of this regimen was rising creatinine occurred in 21% of patients[15] This problem was not encountered in our study, which may be explained by racial difference and small sample size.

Conclusions:-

1-Combined Deferoxamine- deferasiraox therapy proved to be efficient and with insignificant negative effect on renal, hepatic function and platelets.

2-The rate of reduction of serum ferritin is higher for patients on combined group with significant statistically.

3-This approach of therapy is a flexible regimen, which would allow the clinicians to reduce the nightly Deferoxamine injections and increase the oral dose. The only disadvantage of this regimen is the absence of gap free iron chelator time.

Recommendations:-

1-The combined therapy of Deferoxamine-Deferasiraox is safe and convenient with better patient compliance.

2-Larger group of patients need to be restudied for better evaluation depending on liver iron concentration and asses long term outcomes for safety and efficacy of combined therapy Deferoxamine-Deferasirox therapy.)

3- Serum ferritin may not be an accurate predictor of liver iron store in SCD especially in the range of 1500-3000ng/ml and a better parameter for noninvasive estimation is transfusional iron load(TIL) , TIL of more than 100 mg/kg has been closely correlated with high liver iron stores and liver fibrosis. However the imaging techniques which are not available in Iraq like Superconducting Quantum Interference Device (SQUID) and T2* MRI have been developed and validated.

Competing interest: The authors declare that have no competing interests.

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