Combined Deferoxamine - Deferasirox In Treatment Of Thalassemia Major With Iron Overload

الدسفروكسامين والدسفرسيراكس علاج الحمل الحديدي لدى مرضى الثلاسيميا بالعلاج

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الخلاصة:

الهدف : لتقييم فعالية ودرجة الأمان بين نظام علاج الدسفروكسامين- الدسفروسيروكس وعلاج الدسفروسيروكس لوحده لدى مجموعة من مرضى الثلاسيميا .

المنهجية: اثنان وأربعون مريض قسّموا إلى مجموعتين، (٢٩) مريضا المستمرون أصلا على علاج الدسفيروسيروكس٤٠مغ|الكل كغ لليوم لوحده ، و (١٣) مريضا بعلاجالدسفيروسيروكس٤٠ مغ|كغ|باليوم ،سبعة أيام بالأسبوع مع الدسفروكسامين٢٠ مغ|كغ|تحت الجلد خلال ١٢ ساعة ،يومان اسبوعيا لمدّة سَنَةٌ واحدة. كفاءة العلاج قيمت بنسبة الفريتين . والأمان قيّمَ بالمراقبة المتكرّرةِ مِنْ إنزيماتِ لكبدِ وكرياتينين.

النّتائج :بعد سَنَةٍ واحدة مِنْ العلاج لوحظ تخفيضها بممتوسط الفريتين من(٤٤٨٢) الى (٣١٣٢).

الاستنتاج: العلاج المشترك الدسفروكسامين والدسفروسيروكس فعال للحفاظ على طرح الحمل الحديدي

التوصيات :الحاجة لعمل محاولات علاجية اخرى تشمل عدد اكثر من المرضى ولفترة اطول من الزمن مع الاستمرار بالاعتماد على عقارالدسفروسيراكس كعلاج امن وفعال مع مطاوعة جيدة من قبل المرض.

Abstract :

Aim :to assess the efficacy and safety of combined Deferoxamine-defeosiraxregime and deferasiraox alone in group of thalassemia major patients

Patients and Method: Fortytwo patientsstudied for one year.,29 patients of Deferoxamine (20mg/kg/day infusion ,two days /week) and Deferasiraox. Efficacy of both regimes assessed by serum ferritin. safety assessed by liver enzyme, creatinine and blood urea.

Results: Those patients who were on Deferasiraox alone showed significant them chosen fordeferasiraox (40 mg/kg/day),13 patients combinedtherapy reduction of serum ferritin (4482), to meanof serumferritin (3132±336) range (595-8743 ng/l).The study clarified no significant changes in liver enzymes and blood urea, fortunately decline in (ALT), from mean value of (82_+16IU), tomean value (56_+6IU).

Conclusion: combined Deferosirax-Desferoxamine therapy is effective regime to maintained negative iron balance owing to more time iron chelation coverage, and acceptable compliance.

Recommendation:-more clinical trial therapy needs to be done on larger group of patients, and for longer period of time to insure the safety of combined therapy.Deferasirox till now proved to be effective and safe enough to be used with great deal of compliance for patients with iron over load.

Key wards: iron over load, chelation,thalassemia

INTRODUCTION

Haemoglobinopathies such as sickle cell anemia and thalassemia are examples of diseases requiring chronic blood transfusion. If left untreated, iron over load may result in sever morbidity (such as cardiac disease, diabetes, osteoporosis, liver damage) and early mortality. [(1)]Iron overload is an inevitable problem in major thalassemia patients. Every unit of packed blood cell contains 200 - 250 mg iron [(2-3)]The body has no active mechanism to excrete accumulated iron. Iron overload can cause tissue damage such as heart failure, liver disease, endocrine disturbances, which could cause eventual death.[(4-5)]

There have been established evidences that iron chelating drugs reduce tissue damages and improve life expectancy in these patients.[6]

These patients require a continuous iron chelating drugs. The aims of iron chelating therapy in these patients are; first, reducing iron burden, secondly, reducing risk of tissue damage especially in specific key organs such as heart and liver, thirdly, improve life survival, fourthly, provide 24-hour protection from the toxic effects of iron such asLabile Plasma Iron, finally,reduce gap free of iron chelating drugs.[7]

Deferoxamine (DFO) has until now been considered the treatment of choice for patients with chronic iron overload. [8]In recent years multiple different iron chelating regimens were used, which include:monotherapy, combined and alternative sequential regimens.[9-10]Deferasiraox is an orallytaken iron chelator that has been developed for the management of transfusion overload. Its safety, tolerability, and efficacy in reducing iron burden have been demonstrated in patients with thalassemia major. Compliance with the administration of parenteralDeferoxamine therapy has proven challenging to all groups of patients with transfusion over load, [11.]

AIM OF STUDY;

to assess safety and efficacy of combined DFO-DFX therapy versus DFX alone in thalassemia patients

PATIENTS AND METHOD

This is prospective, comparative study done in AL Najaf thalassemia center, fromJanuary 2011, until the end of January 2012. Patients enrolled in this study were 42 of transfusion dependent.

Twenty nine (29) patients were chosen to start oral (DFX) therapy randomly by way of (2:1) sequence of their files .Starting oral dose was 30/mg/kg day, beforebreakfast, increasedgradually by 5mg/kg/month to maximum of 40 mg/kg/day.

Thirteen (13) patients were already on (DFO) therapy on adose of 20 mg/kg/day, subcutaneously infused by special portable device, 12 hour aday, five days /week. When they were chosen to enter this study, their therapy changes to combined (DFO) 20mg/kg/day infusion two days per week, and (DFX) in dose of 40 mg/kg/day seven days per week.

Written consents were taken from patients or parents who chose combined therapy, and the draw back of each drugs were clarified for all patients in both group.

Serum ferritin level of those who were on DFX alone at the start of the study was in the range (1148-10450 ng/ml), while ferritin level of those who chose combined therapy, at the start of the study, was in the range (6175-10800 ng/ml).

For all studied sample, Cell Blood Count (CBC), serum ferritin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), BUN, urinalysis, visual and auditory examination and echocardiography were tested before treatment and each month throughout the treatment period.

Patients were excluded if they had a serum creatinin above the upper limit of normal or active hepatitis.

Safety of both drug regimens was monitored by monthly assessment of liver enzymes. Bloodurea, serumcreatinin level and prothrombine time.

After collecting data, statistical analysis was performed by SPSS 16.0.2. Differences were considered significant at P <0.05.

RESULTS

There was no significant adverse effect in both drug regimen, leading to discontinuation of treatment& there was no patient loss during one year follow up. Haemoglobin level of all patients was maintained between (8.6-9.8gm/dl).Adverse side effects in (7)patients(17.5%)receiving either treatment, arenotified, these events observed in four(4)patients taking DFX,and in three patients taking combined DFO-DFX therapy. These adverse events include: some bouts of abdominal pain, diarrhea, cough, itching, and back pain. Flu like illness was noticed in two patients on combined therapy, may be related to exposure to cold during winter.

Regarding alanine aminotransferase (ALT), level fortunately showed some decline in those who were on monotherapy (82±16 IU/l) at the start and 56±6 IU/lat the end), P value was not significant, while in those patients who were on combined therapy, slight elevation of ALT (62 IU/l) to (68IU/l) was noticed after one (P-value was not significant) {table1}

For those who were on combined therapy, there was no significant difference in the level of ALT noticed at theend of the study.

Regarding prothrombine time(PT) and aspartate aminotransferase (AST)in both group, all reading were maintained within permitted levels ,and there was no significant surgenoticed for all reading,p value was not significant for the mean SD in both groups.

Serum creatinine (SC) and blood urea (BU) level maintained within normal level, means SD, were(0.4±2 and 27±3)respectively, for both groups.[table1]

Fortytwo(42) patients were chosen to enter both type of treatments,29 patients continued on oral DFX ,at the start, their serum ferritin range from(1148-10450ng/ml),meanSD(4482±425ng/ml).At the end of the study, mean serum ferritin was reduced to, meanSD (3132±336) with a range (595-8743ng/ml).[table1]

Table 2;demonstrate thatthe mean pair deference between mean serum ferritin level at the start ,and its mean level at the end of the study was(1350±227),confidenceinterval(95%) of which, lies between serum ferritin level (884-1815) and the p-value is statically very significant(0.001).

Thirteenpatients (13) chosen randomly for combined DFO-DFX therapy. Serum ferritin rangewas (6175-10800 ng/ml), meanSD (8601±352), at the end of the study serum ferritin maintained between (4215-8934ng/ml), meanSD (6656±384) and the p value is very significant.[table1]

The pair deference between the two serum ferritin, means SD at the start and the end is (1945±277), with confidenceinterval (95%), lies between (1346-2544 ng/ ml)[table3]

Those patients, who were on combined therapy, demonstrated more reduction in serum ferritin (1945±277ng/ ml)[table3] than those who were on deferasirox alone (1350±227ng/ ml) and p value was statically significant (0.01).[table 2]

Table 1; changes in deferent variable over one year for patients in both groups

variable over one year for patients on DFX					variable over one year for patients on combined therapy		
	variable	Mean	no	Std. Error Mean	Mean	no	Std. Error Mean
Pair 1	sfer1	4482.9310	29	425.36411	8601.5714	13	352.446
	sfer2	3132.7241	29	336.17471	6656.0714	13	384.644
Pair 2	BU1	30.5172	29	3.03102	27.5714	13	2.3457
	BU2	28.4310	29	2.03513	26.7143	13	1.6152
Pair 3	ALT1	82.5517	29	16.05813	62.4107	13	0.463
	ALT2	56.4138	29	6.53477	68.4500	13	0.066
Pair 4	AST1	91.9310	29	12.88142	49.1429	13	4.036
	AST2	93.5172	29	13.15038	56.7857	13	6.238
Pair 5	PT1	13.8966	29	0.20064	12.1429	13	0.3315
	PT2	13.1379	29	0.48047	13.0000	13	0.7875
Pair 6	SC1	0.421	29	0.001	0.4107	13	0.014
	SC2	0.502	29	0.021	0.4500	13	0.021

(1)=start of therapy (2)=At the end of study (PT)prothrombine time (SC) creatinine-(BU)blood urea---(S Fer) serum ferritin

This table clarified the degree of decrement of serum ferritin in both group, between the time at the start and the end of study. Changes in liver and renal indices is well stated which remain within acceptable safe level.

Table 2; paired sample test for mean SD of all variable at the start and end of study for patients on DFX treatment

	Paired difference	95% confidence interval of difference		t	pt.	Sig P value
		Lower	upper			
S Fer 1 – S Fer 2	**1350.206**	**884**	**1815**	**5.9**	**29**	**0.00**
BU 1---BU 2	**0.0862**	**-0.021**	**-194**	**1.636**	**29**	**0.113**
ALT1 --ALT2	**26.137**	**15.906**	**-6.444**	**1.643**	**29**	**0.112**
AST1—AST2	**-1.586**	**5.957**	**-13.7**	**-0.266**	**29**	**0.792**
PT1—PT2	**0.7586**	**0.5077**	**-.2813**	**1.494**	**29**	**0.146**

SC 1 –SC 2	**-0.180**	**0.301**	**0.422**	**0.238**	**29**	**0.123**

This table demonstrate the paired deference for serum ferritin for those who were on DFX therapy , liver, and renal variable .p value is only significant for ferritin deference(0.00).

Table 3; paired sample test for mean SD of all variable at the start and end of study for patients on DFO-DFX treatment

	Paired Differences			t	pt	P value
		95% Confidence Interval of the Difference				
	Mean difference	Lower	Upper			
sfer1 - sfer2	1945.5	1346.6	2544.3	7.018	13	.000
BU1 - BU2	.85714	-4.62440	6.33869	.338	13	.741
ALP1 - ALP2	-.403929	-.20731	.12874	-.505	13	.622
AST1 - AST2	-7.64286	-27.54580	12.26008	-.830	13	.422
PT1 - PT2	-2.42857	-18.43863	13.58149	-.328	13	.748
SC1 – SC2	- 0.0380	0.253	0.412	-0.123	13	.342

The mean difference and 95%confidence interval is only significant for changes in serum ferritin at start and the end of study, while for renal and hepatic changes remain with nonsignificat changes for group using combined therapy.

DISCUSSION

Iron chelation therapy is lifelong requirement for thalassemic patients who were transfusion dependent, but till now, there was limited publisheddata, from prospective clinical trial in pediatricpatient's clarified efficacy and safety of long term treatment. Deferoxamine (DFO) has been the standard iron chelator since the 1970s. DFO is both safe and effective for transfusionhemosiderosis. A hexadentatechelator, it binds iron tightly, and the iron-DFO complex is excreted in both urine and stool. Monotherapy with Deferoxamine needs an electronic pump for slow infusion over 8-12 hours, 5 to7 nights per week [(12)]. So, for long period patients were not complied well with lifelong subcutaneous therapy.[(13,14).]

The other iron chelator drug is Deferasirox, has a half-life of 8-16 hours, and like DFO is unable to provide 24-hour chelating coverage. Monotherapy have not achieved all therapeutic goals because of short half livesof these medicines (20-30 minutes for DFO and 8-16 hours for Deferasirox) and rapid decline in plasma levels.[(12)]Deferasirox was generally well tolerated over the long term in bothpediatric and adult patients. It is a once-daily oral iron chelator that has proven effective in reducing liver iron concentration and serum ferritin levels over one year in patients with transfusion dependent anemia. [(15)]

There was limitedpublisheddata that highlight the efficacy and effect of combined usage of oral iron chelatordeferasirox and subcutaneous deferoxamine, although there was no apparent drawback of using both drugs since each compound has different way of metabolism and elimination from the body.Regarding the safety of oral chelator,Rheault MN ea al had reported Fanconi-like syndrome in the kidney during deferasiroxtreatment [(16)], a condition which was not reported in our study, nevertheless, its safety regarding effect on serum creatinine and blood urea was very clear in this study, even with sustained dose of deferasirox (40mg/kg/day) throughout one year period.Although it is known that deferasirox had tendency to increase liver

enzymes, in particular in patients with high liver iron concentrations [17] in our studyitseffect liver enzymes was notsignificant, on the contrary therewas some improvement in AST, as shown in table 2 .Cohen AR, notifiedthat, none of iron chelator drugs could provide all therapeutic goals in transfusion dependent thalassemia patients based on monotherapy approach.[18]Our study demonstrated significant change in serum ferritin, throughout one year period,the mean SD of serum ferritin level reduced from (4482±425ng/ml) to (3132±336ng/ml) with p-value 0.001. Combined DFO (20 mg/kg/day, 2days/wk.) and DFX therapy (40 mg/kg/day, 7 days per week) have shown maintained significant and safe decline in mean serum ferritin(8601±352)to (6656±384 ng/ml)with no clear changes in hepatic or renal function.Combination therapy first practiced in major thalassemia by Anderson et al. They used combination Deferoxamine / Deferiprone and proposed several potential advantages with this regimen [19]. Medicines with different properties and mechanisms may access different iron pools. The molecule of Deferasirox is small and can easily enter into cells and is able to transfer iron into plasma for Deferoxamine chelation.[20]This approach of therapy is a flexible regimen, which would allow the clinicians to reduce the nightly Deferoxamine injections and increase the oral doses with high efficacy and low toxicity.In present study serum ferritin decreased significantly in both groups of studied patients. Combined regimen was associated with minimal adverse effect as it was showed by insignificantchanges in liver enzymes, PT, BU and Serum creatinine.KeikhaeiBdhadshown significant elevation of serum creatinine in 21% of patients studiedwith sequential DFO-DFX regimen, although creatinine rising were in normal limits. It was reported that in monotherapy approach this adverse drug reaction is high. [21] Combined oraldeferiprone-subcutaneous deferoxamine had shown significant improvements in in cardiac function in thalassemia patients with heart failure. [22]Our study revealed that the difference in mean serum ferritin between its level at the start,and at the end of the study was significant in both studied group, but still those who were oncombined therapy, demonstrated more reduction in serum ferritin (1945±277ng/ml) than those who were ondeferasiroxalone(1350±227ng/mlandpValue was statisticallysignificant (0.01).In spite of this result still we maintained our confidence in oral chelatorsince it was associated with excellentcompliance, least disturbance in dailyactivities and without pain associated with injection even with two days per week protocol in this study.

LalA et alclarified that simultaneous administration of DFO and DFX rapidly reduced systemic and myocardial iron, and provided an excellent control of the toxic labile plasma iron species without an increase in toxicity. His clinical trial done to evaluate the safety and efficacy of combined therapy with deferasirox (DFX, 20-30 mg/kg daily) and deferoxamine (DFO, 35-50mg/kg on 3 days/week) in 22 patients with persistent iron overload or organ damage.[23]

Combined Deferoxamine -deferasiroxare a new protocol to date with advantages of more time iron chelator coverage, acceptable efficacy and compliance and lower side effects. This new protocol still need more clinical trial to be done on larger target group in order to insure its safety and efficacy, so that perfect benefit insured for those patients with iron overload with serious life threatening complications.

CONCLUSIONS

1-combined DFX-DFO therapy is effective regime to maintained negative iron balance in thalassemia with iron overload owing to more time iron chelatorcoverage, and acceptable compliance.

2-combined protocol issafe, with no significant adverse effect on general condition of patients.

RECOMMENDATIONS

1-more clinical trial therapy needs to be done on larger group of patients, and for longer period of time to insure the safety of combined therapy,

2-Deferasirox till now proved to be effective and safe enough to be used with great deal of compliance for patients with iron over load.

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