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Pegylated erythropoietin and darbepoetin Alfa: A study on comparison of renal parameters among CKD patients on maintenance hemodialysis

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Abstract
Chronic inflammation is a common feature of CKD and is a major cause of its associated morbidity and mortality. Erythropoiesis is inhibited by several pro-inflammatory cytokines such as interleukin-1, tumor necrosis factor-alpha (TNF-α) and interferon gamma (IFN-γ).[12] These cytokines are particularly involved in the inflammatory process as they are directly produced by macrophages (TNF-α, IL-1) or because their production by another cell is induced by a macrophage cytokine (IFN-γ). Several studies have shown that markers of inflammation are associated with a decreased response to erythropoietin. Out of these 52 patients, 12 patients couldn't complete the study. 5 patients (2 in group A and 3 in group B) left the study in between due to some unknown causes and 7 patients (4 in group A and 3 in group B) expired during the study.So finally 40 patients (20 in each group) completed the study. In group A there was a slight decrease in systolic and diastolic blood pressure from baseline values of 153.5±12.06 and 92.3±6.06 mm of Hg to 150.4±12.62 and 89.2±5.36 mm of Hg at 3 months, but the decrease was not significant statistically ($p > 0.05$). In group B also there was a slight decrease in systolic and diastolic blood pressure from baseline values of 156.2±8.72 and 92.4±6.31 mm of Hg to 149.1±18.20 and 93.6±4.75 mm of Hg at 3 months, but the decrease was not significant statistically ($p > 0.05$).
Keywords: Pegylated erythropoietin, darbepoetin alfa, CKD

Introduction
Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiological processes associated with abnormal kidney function and progressive decline in glomerular filtration rate. It is an important, chronic, non-communicable disease epidemic that affects the world, including India. It is a global threat to health in general and for developing countries in particular, because therapy is expensive and life-long. Incidence of CKD has doubled in the last 15 years. Data from the United States Renal Data System (USRDS) show that incidence of kidney failure is rising among adults and is commonly associated with poor outcomes and high cost. An analysis of federal health data found that 13 percent of American adults-about 26 million people-have chronic kidney disease, up from 10 percent, or about 20 million people, a decade earlier. There are ~1.8 million people in the world who are alive simply because they have access to one form or another of renal replacement therapy[1, 2].
The role of chronic inflammation and proinflammatory cytokines in erythropoietin hyporesponsiveness is gaining increased recognition. Chronic inflammation is a common feature of CKD and is a major cause of its associated morbidity and mortality. Erythropoiesis is inhibited by several pro-inflammatory cytokines such as interleukin-1, tumor necrosis factor-alpha (TNF-α) and interferon gamma (IFN-γ)[3].These cytokines are particularly

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involved in the inflammatory process as they are directly produced by macrophages (TNF-α, IL-1) or because their production by another cell is induced by a macrophage cytokine(IFN-γ). Several studies have shown that markers of inflammation are associated with a decreased response to erythropoietin. Furthermore, high plasma concentrations of C-reactive protein (CRP) have shown to be associated with anemia and ESA hypo responsiveness in chronic hemodialysis patients. Recently Chonchol M *et al*.showed that while anemia is closely associated with a reduction in estimated GFR (eGFR) levels, much of this association appears to be the result of confounding by associated factors, especially the presence of chronic inflammation as reflected by increased plasma Hs-CRP concentrations[4].Furthermore, these inflammatory markers have been shown to predict lower hemoglobin concentrations in patients on dialysis and to be responsible for ∼10% of the observed variability in the ESA dose requirements. Inflammation-induced anemia and resistance to erythropoietin are common features in patients with advanced CKD. Proinflammatory cytokines can also influence the response of erythropoietin through disruption of iron metabolism. Hypoferritinemia is often observed in presence of infection or inflammation despite adequate iron stores which is a consequence of impaired release of iron from the monocyte macrophage system. Elevated levels of inflammatory cytokines enhanced oxidative stress and alterations in iron metabolism-conditions associated with inflammatory states-may be implicated in the development of anemia. INF-γ and TNF-α diminishes colony formation of burst-forming unit-erythroid cells (BFU-Es) and colony-forming unit-erythroid cells (CFU-Es) and exacerbate anemia. The marked inhibitory effects of these inflammatory cytokines on erythroid progenitor cells may be mainly related to the ability of these cytokines to decrease endothelial nitric oxide production, which is known to stimulate the proliferation of erythroid progenitor cells. Inflammation is usually attributed to blood-dialyzer interactions, impurities within the dialysate or other coexisting co morbid diseases with ESRD[5, 6].

Methodology

103 Patients of CKD who were undergoing regular maintenance hemodialysis in nephrology department in this institute were screened. All these patients were receiving injection Recombinant Human Erythropoietin (rHuEPO) 4000 I.U. subcutaneously twice weekly and injectable iron in a dose of 100 mg/week following dialysis session. The patients were observed for one month and rise in hemoglobin values were seen for each patient. Out of these 103 patients, 61 were found to have inadequate rise in Hb (< 1g/dl rise in Hb in one month). The dose of erythropoietin was increased to 6000 I.U. S/C twice weekly and response was seen after one month. 8 patients showed good response to increased dosage of erythropoietin and were excluded from the study. One patient developed lower G.I. bleeding due to haemorrhoids and was also excluded. So, final group of 52 patients were labelled as erythropoietin resistant. These 52 patients were randomly divided into two groups A and B. Group A included 26 patients and Group B included 26 patients. Group A was given pegylated erythropoietin (0.6 mcg/kg body weight, s/c) onceintwoweeks and i.v iron 100 mg/week, afterthehemodialysissession, for 3 months. Group B was given darbepoetin alfa (0.45 mcg/ kg body weight, s/c) once weekly and i.viron100 mg/weekafterthehemodialysissessionfor3months.

Out of these 52 patients, 12 patients couldn't complete the study. 5 patients (2 in group A and 3 in group B) left the study in between due to some unknown causes and 7 patients (4 in group A and 3 in group B) expired during the study.So finally 40 patients (20 in each group) completed the study.

Inclusion criterion

1. Adult patients of CKD on maintenance haemodialysiswho are anemic (Hb < 9 gm/dl) and despite receiving erythropoietin in a dose of 4000 I.U. S/C twice weekly and injectable

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iron 100mg/week for 2 months, showing no improvement in haemoglobin levels or requiring increase in erythropoietin dose to maintain Hb level > 9 gm/dl.

Exclusion criterion

1. Patients having chronic inflammatory conditions like arthritis.
2. Patients who are pregnant.
3. Patients with H/O chronic blood loss (i.e. haemorrhoids, actively bleeding peptic ulcer).
4. Patients with hemochromatosis /hemoglobinopathies/vitamin B12 & folate deficiency.
5. History ofseriousorsevere allergicreactions.
6. Uncontrolledhypertension.

A total of 40 adult patients of CKD fulfilling the above criteria andconsenting for the study were enrolled. Each patient was subjected to detailed history and physical examination and investigations were carried out at thebeginningof the study.

Results

Follow up ofbiochemical parameters in group A (Table 16) revealed a change in mean blood urea to be112.25±16.58, 108±16.62, 103.3±16.34, 99.95±13.20 mg% at baseline, 1 month, 2 months and 3 months, respectively and the fall in mean blood urea was statistically significant ($p < 0.05$). Mean creatinine was 5.87±1.29, 5.86±0.93, 5.43±0.94 and 5.10±0.98 mg% at baseline, 1 month, 2 months and 3 months, respectively and the fall in mean creatinine was statistically significant ($p<0.05$). Mean phosphate was 6.31±1.01, 6.26±1.14, 5.95±0.90 and 5.64±0.74mg % at baseline, 1 month, 2 months and 3 months, respectively and the fall in mean phosphate was statistically significant ($p<0.05$). Change in mean uric acid was 6.99±0.88, 6.92±0.86, 6.69±0.79, 6.52±0.72mg% at baseline, 1 month, 2 months and 3 months, respectively and the fall in mean uric acid was statistically significant ($p<0.05$). Mean ferritin was 603.40±226.13, 549.65±180.76, 497.30±142.57, 457.35±120.45 ng/ml at baseline, 1 month, 2 months and 3 months respectively and the decrease in ferritin level was found to be statistically significant ($p < 0.001$). Similarly, mean transferrin saturation was 18.24±1.11; 23.31±0.99, 29.19±2.62 and 34.21±3.25% at baseline, 1 month, 2 months and 3 months respectively and the increase in transferrin saturation was also found to be statistically significant ($p < 0.001$). On performing repeated measures ANOVA, the change in other parameters were not significant statistically ($p > 0.05$) when followed for 3 months, as shown in table below.

Table 1: Change in biochemical parameters during the study in group A

Parameters	Baseline (Mean± S.D.)	At 1 Month (Mean± S.D.)	At 2 Months (Mean± S.D.)	At 3 Months (Mean± S.D.)	ANOVA (P value)
B.Urea (mg %)	112.25±16.58	108.00±16.62	103.3±16.34	99.95±13.20	0.04
S.Creatinine (mg %)	5.87±1.29	5.86±0.93	5.43±0.94	5.10±0.98	0.03
S.Sodium (meq/l)	141.90±6.7	140.75±4.39	140.05±3.4	136.05±3.90	0.705
S.Potassium (meq/l)	4.73±0.85	4.71±0.44	4.55±0.42	4.50±0.48	0.447
S.Calcium (mg %)	8.04±0.43	8.05±0.37	8.02±0.40	8.08±0.18	0.935
S.Phosphate (mg %)	6.31±1.01	6.26±1.14	5.95±0.90	5.64±0.74	0.04
S.Uric Acid (mg %)	6.99±0.88	6.93±0.86	6.69±0.79	6.52±0.72	0.02
S.Protein (g/dl)	6.36±0.61	6.27±0.47	6.36±0.54	6.40±0.51	0.827
S.Albumin (g/dl)	3.80±0.80	3.71±0.73	3.75±0.76	3.80±0.69	0.846
Proteinuria (g/day)	1.20±0.54	1.11±0.45	1.20±0.39	1.20±0.39	0.836
GFR (ml/min/1.73m²)	7.28±3.04	7.71±2.84	7.65±2.84	7.53±2.9	0.935
Ferritin (ng/ml)	603.40±226.13	549.65±180.76	497.30±142.57	457.35±120.45	<0.001
Transferrin saturation (%)	18.55±1.41	23.31±0.99	29.19±2.62	34.21±3.25	<0.001

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Follow up of biochemical parameters in group B revealed a change in mean blood urea to be 112.45±13.08, 109.85±14.95, 109.75±9.47 and 107.4±11.37 mg% at baseline, 1 month, 2 months and 3 months, respectively and the decrease wassignificant statistically on applying repeated measures ANOVA ($p < 0.05$). Mean creatinine was 6.72±0.85, 6.08±1.31, 5.93±1.07 and 5.77±1.27mg% at baseline, 1 month, 2 months and 3 months, respectively and the decrease was significant statistically ($p < 0.05$). Change in mean uric acid was 7.41±1.76, 7.11±1.06, 7.14±0.93 and 7.06±0.99 mg% at baseline, 1 month, 2 months and 3 months, respectively and the fall was significant statistically ($p < 0.05$). Mean phosphate was 6.11±1.78, 6.31±1.2 mg, 6.47±1.12 and 6.14±0.99% at baseline, 1 month, 2 months and 3 months, respectively (<0.05) and the fall was significant statistically ($p < 0.05$). Mean serum ferritin was 576.85±235.2, 601.25±267.1, 635.75±302.7,664.7±292.71ng/ml at baseline, 1 month, 2 months and 3 months and increase in ferritin level was found to be statistically significant ($p = 0.001$). Mean transferrin saturation was 18.69±1.40, 18.73±1.00, 19.03±1.22, 19.86±1.61% at baseline, 1 month, 2 months and 3 months but the increase in transferrin saturation was not significant statistically ($p > 0.05$). The change in all other parameters were not significant statistically ($p > 0.05$) during the follow up of 3 months.

Table 2: Change in biochemical parameters during the study in group B

Parameters	Baseline (Mean± S.D.)	At 1 Month (Mean± S.D.)	At 2 Months (Mean ± S.D.)	At 3 Months (Mean± S.D.)	ANOVA (P value)
B.Urea (mg %)	112.45±13.08	109.85±14.95	109.75±9.47	107.5±11.37	0.03
S.Creatinine (mg %)	6.72±0.85	6.08±1.31	5.93±1.o7	5.77±1.27	0.04
S.Sodium (meq/l)	142.2±5.28	139.75±4.51	137.9±3.21	140.15±4.8	0.234
S.Potassium (meq/l)	4.59±0.93	4.58±0.49	4.50±0.56	4.43±0.58	0.851
S.Calcium (mg %)	8.01±0.38	8.26±0.6	8.31±0.37	8.26±0.5	0.184
S.Phosphate (mg %)	6.11±1.78	6.31±1.2	6.47±1.12	6.14±0.99	0.04
S.Uric Acid (mg %)	7.41±1.76	7.11±1.06	7.14±0.93	7.06±0.99	0.03
S.Protein (g/dl)	6.26±0.31	6.14±0.28	6.50±0.46	6.52±0.45	0.287
S.Albumin (g/dl)	3.59±0.44	3.70±0.49	3.76±0.42	3.71±0.44	0.621
Proteinuria (g/day)	1.30±0.63	1.32±0.63	1.31±0.47	1.34±0.54	0.997
GFR (ml/min/1.73m²)	7.72±3.26	8.27±3.7	7.05±2.55	7.31±2.69	0.631
Ferritin (ng/ml)	576.85±235.2	601.25±267.1	635.75±302.7	664.7±292.71	0.001
T. saturation (%)	18.69±1.40	18.73±1.00	19.03±1.22	19.86±1.61	0.810

Comparative analysis of blood urea between the two groups revealed no statistically significant difference at baseline, at 1 month, at 2 months and 3 months ($p > 0.05$). When serum creatinine levels were compared, no statistically significant difference was observed between the two groups at baseline, at 1 month, at 2 months and at 3 months of study ($p > 0.05$). Similarly on comparing serum uric acid there was no statistically significant difference between the two groups at baseline, at 1 month, at 2 months and at 3 months of study ($p > 0.05$). But the difference between the two groups in blood urea, serum phosphate, serum uric acid & serum phosphate was found to be statistically significant at the end of 3 months of study ($p < 0.05$) i.e., the fall in the level of above renal parameters was higher in group A as compared to group B at 3 months of study.

Table 3: Comparison of renal parameters between the two groups at monthly interval**

Parameters		Baseline (Mean±S.D)	At 1 Month (Mean±S.D)	At 2 Months (Mean±S.D)	At 3 Months (Mean±S.D)
Blood urea(mg %)	Group A	112.25±16.58	108.35±16.62	103.3±16.34	99.95±13.20
	Group B	112.45±13.08	109.85±14.95	109.75±9.47	107.4±11.37
	P value	0.940	0.748	0.141	0.04
Serum creatinine (mg %)	Group A	5.87±1.29	5.86±0.93	5.43±0.94	5.10±0.98

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	Group B	6.72±0.85	6.08±1.31	5.93±1.07	5.77±1.27
	P value	0.377	0.527	0.126	0.04
Serum uric acid (mg %)	Group A	6.99±0.88	6.92±0.86	6.69±0.79	6.52±0.72
	Group B	7.41±1.76	7.11±1.06	7.14±0.93	7.06±0.99
	P value	0.339	0.537	0.103	0.04
Serum phosphate (mg %)	Group A	6.31±1.01	6.26±1.14	5.95±0.90	5.64±0.74
	Group B	6.11±1.78	6.31±1.2	6.47±1.12	6.14±0.99
	P value	0.666	0.926	0.112	0.04

In group A there was a slight decrease in systolic and diastolic blood pressure from baseline values of 153.5±12.06 and 92.3±6.06 mm of Hg to 150.4±12.62 and 89.2±5.36 mm of Hg at 3 months, but the decrease was not significant statistically (p >0.05). In group B also there was a slight decrease in systolic and diastolic blood pressure from baseline values of 156.2±8.72 and 92.4±6.31 mm of Hg to 149.1±18.20 and 93.6±4.75 mm of Hg at 3 months, but the decrease was not significant statistically (p >0.05).

Table 4: Blood pressure during the study in both groups

Duration of study	Group A		Group B	
	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
Baseline	153.5±12.06	92.3±6.06	156.2±8.72	92.4±6.31
1 month	153.4±9.24	90.5±6.11	153.4±10.28	89.9±4.32
2month	153.6±9.72	89.4±4.59	151.2±16.51	89.5±8.07
3months	150.4±12.62	89.2±5.36	149.1±18.20	93.6±4.75
ANOVA(P value)	0.722	0.237	0.457	0.134

Discussion

Darbepoetinalfaisanerythropoiesisstimulating165 amino acidproteinproducedbyrecombinantDNAtechnology, whichdiffersfromtheendogenouserythropoietin bycontainingtwomoreN-linkedoligosaccharidechain.Duetoits3foldlongerhalf-lifeandgreaterbiologicalactivitythanrecombinanthumanerythropoietin (rHuEpo),darbepoetinalfamaintainseffectivehaemoglobincontrolatextendeddoseintervalscomparedtorHuEpo[7].

AstudyconductedbyR Brunkhorst*et al*.showedthatdarbepoetinalfaeffectivelymaintainedhemoglobinconcentrationsatanextendeddoseintervalrelativetointravenousorsubcutaneousrecombinanthumanerythropoietinindialysispatients.Inthismulticentre, prospective,open label, single-armstudy,1502patientsofchronickidney diseaseondialysiswereevaluatedfortheefficacyandsafetyofunitdosesofdarbepoetinalfaadministeredeitheri.vorsubcutaneously. Aftera2 week screening, subjectswereswitchedfromrHuEpotodarbepoetinalfaatanextendeddoseintervalbutusingthesamerouteofadministration.

Itwasfoundthatfollowingi.vadministration,themeanhemoglobinconcentrationduringtheevaluationperiodincreasedby0.19 g/dl comparedwithbaseline, themeanchangein

hemoglobinconcentrationfrombaselinetotheevaluationperiodfollowingsubcutaneousadministrationwas-0.02 g/dl andwithregardtofrequencyofadministration,themeanchangeinhemoglobinconcentrationfrombaselinetoevaluationperiodwas +0.14 g/dl insubjectsreceivingdarbepoetinalfaonceaweekand-0.13 g/dlin subjectsreceivingdarbepoetinalfaonceeverytwoweeks.Theseresultsconcludedthatunitdosingwithdarbepoetinalfacaneffectivelyandsafelymaintainhemoglobinconcentrationswithina targetrangeafterswitchingfromrHuEpo atextendeddoseinterval[8, 9].

AprospectiverandomizedtrialconductedbyAl-Ali *et*

al.showedthatoncemonthlyC.E.R.AwaseffectiveinmaintainingHblevelscomparedtoerythropoietinalfaanddarbepoetinalfa. In thisstudy,327chronic kidneydisease patientswithanemiaonerythropoietinalfaorbetawererandomizedintothreedifferenttreatmentgroupsthatiseithertocontinueonthepreviousregimenoferythropoietinortoreceivedarbepoetinalfaor C.E.R.Aforatotalof40weeksanditwasobservedthatthepercentageofpatientswhoachievedthetargetHbrange(11-12g/dl) wasconstantlyabove 50%among C.E.R.AgroupandtherewasasignificantlylowermeannumberofdoseadjustmentsinC.E.R.Agroup comparedtoothertwogroups(p=0.001)[10].

Thustherearevariousstudiesonthebeneficialeffectsofeachofthesecondandthirdgenerationerythropoiesis

stimulatingagentsseparatelyandonlyaveryfewstudieswhichcomparetheeffectofboththeagentssimultaneouslyon

patientswithepohyporesponsiveness.Theresultsarealsovariedandnostudyhasbeendone inIndiatilldate.HencethepresentstudyisdesignedtoknowtheeffectsofpegylatederythropoietinanddarbepoetinalfaonanemiaofchronickidneydiseasepatientsonhemodialysiswithEpohyporesponsiveness.

Conclusion

In this study there was gradual reduction in blood urea, serum creatinine, serum uric acid and serum phosphate from baseline to values at 3 months in both the groups, which was statistically significant, which reflected the adequacy of hemodialysis and the changes in serumsodium, serum potassium, serum calcium, serum proteins, iPTH, proteinuria and GFR, blood pressure in both the groups were not found to be statistically significant.

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