

# Exciting results with injection darbepoietin alfa and pegfilgrastim in patients with decompensated liver cirrhosis

## Abstract

**Introduction:** Dysregulated erythropoietin (EPO) plasma levels may play a role in the patho physiology of liver cirrhosis. No report of Darbepoietin alpha and Pegylated Filgrastim use in Liver cirrhosis.

**Aims and methods:** To study the benefits of Darbepoietin and Pegfilgrastim in patients with de-compensated liver cirrhosis. Prospectively clinical data recorded since October 2014. Patients with active bleed, hepato renal syndrome, hepatoma, portal vessel thrombosis were excluded. Patients started on Injection Darbepoietin alpha 200 microgram and Injection Pegfilgrastim 6mg subcutaneously every 15days, total three visits of patients, then three month follow up planned. Improvement in clinical, laboratory parameters analyzed. Median calculated, Wilcoxon Signed-Rank Test applied to compare both groups.

**Results and discussion:** N=22 all male, 3 lost to follow up, aetiology of cirrhosis were Non-alcoholic Fatty Liver Disease 5, Hepatitis B Virus 3, Hepatitis C Virus 2 and Alcohol 12. Median age 59years (range: 40 to 70). Improvement in Haemoglobin from 10.1gram% (range 5.9-13.4gm%) to 10.6gm% (range: 7.5-13.7gm%) p value 0.00374, Total leukocyte count from 5100/cu mm to 7100/cu mm p value 0.00214, Platelet count 90,000/cu mm to 146,000/cu mm, p value 0.00096, INR 1.7 (range 1.5-4.8) to 1.4 p value 0.00064, Albumin 2.4 gram/dl (range 1.6-2.9) to 2.5gm/dl (range 1.8-3.5) P value 0.043, Child score from 10 to 8 P value 0.007, ascites score 2 to 1, P value 0.00222. No significant improvement in Serum creatinine, sodium, potassium, calcium, bilirubin, total protein and hepatic encephalopathy. High cost of medicine was the limiting factor.

**Conclusion:** Our study suggests that Darbepoietin Alpha and Pegfilgrastim is significantly effective in improving hematology, International normalized ratio, Albumin, ascites and Child score of liver cirrhosis patients.

**Keywords:** darbepoietin, pegfilgrastim, liver cirrhosis, albumin, ascites, child score

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**Abbreviations:** HBV, hepatitis b virus; HCV, hepatitis c virus; NAFLD, non-alcoholic fatty liver disease; TLC, total leukocyte count; INR, international normalized ratio

## Introduction

Dysregulated erythropoietin (EPO) plasma levels may play a role in the patho physiology of chronic liver disease (CLD)<sup>1</sup> because chronic anaemia is frequently observed in patients with liver cirrhosis. Some reports have used regular short acting Erythropoietin as well as low dose long acting Erythropoietin and regular short acting Granulocyte colony stimulating factor (Filgrastim) in liver cirrhosis patients with significant benefits to patients.<sup>2,3</sup> There is no report of use of high dose long acting erythropoietin (Darbepoietin Alpha) and pegylated granulocyte colony stimulating factor (Pegfilgrastim) in patients with de-compensated Liver cirrhosis.

## Patients and methods

Prospective pilot study all patients of de-compensated liver cirrhosis giving consent for the study was enrolled, haematological, biochemical, ultrasound, clinical parameters were recorded. Patients with active bleed, confirmed hepato renal syndrome, hepatoma,

portal vein thrombosis, splenic vein thrombosis were excluded. Study started from October 2014 onwards, Patients started on Injection Darbepoietin alpha 200 microgram and Injection Pegfilgrastim 6mg subcutaneously every 15days, total three injections, and minimum Three month follow up planned. Improvement in Haematological, coagulation, biochemical, clinical parameters and Child score was analyzed. Median was calculated for nonparametric variables and continuous variables and Wilcoxon Signed-Rank Test applied to compare both groups.

## Results

Total 22 patients included, 3 were lost to follow up and all 22 patients were male. Etiology of cirrhosis was NAFLD in 5, HBV cirrhosis 3, HCV 2 and Alcohol in 12 patients. Median age of the patients was 59years (range 40 to 70years). There was increase in Haemoglobin from 10.1gram% (range 5.9-13.4gm%) to 10.6gm % (range 7.5-13.7gm%) Z-value is 2.8966. P-value is 0.00374, Total leukocyte count increased from 5100/cubic mm (range 1400-13300) to 7100cubic mm (range 3500-42000) Z-value-3.067. P-value is 0.00214. Platelet count increased from 90,000/cmm (range 14000-260000) to 146,000/cubic mm (37000 to 270000) Z-value is 3.2958.

P-value is 0.00096, International normalized ratio improved from 1.7(range: 1.5-4.8) to 1.4(range: 1.1-3.6) Z-value- 3.4078. p-value-0.00064 and Serum Albumin increased from 2.4gram/dl (range: 1.6-2.9) to 2.5gm/dl (range: 1.8-3.5) (Z value-2.028, P-value-0.043), Child score improved from 10 to 8 (Z-value-3.4078. p-value-0.00064 Z-value-2.694, P-value-0.007) and ascites score improved from 2 to 1 (Z-value is -3.0594. P-value is 0.00222). There was no significant improvement in Serum creatinine, sodium, potassium, calcium, bilirubin, total protein, hepatic encephalopathy. One patient developed fever with respiratory tract infection during treatment, which led to de-compensation, but later improved and high cost of medicine.

## Discussion

Small number of study cohort with three month follow up are the limitations of the study., we studied the Child's Stage classification, which is most commonly used parameter to access the stage of liver disease, survival and prognosis. We recruited only Child's C patient in the study, who need some supportive treatment because liver transplantation was not possible due to socioeconomic and personal reasons. On follow up improvement in Child's score was statistically significant, we could very well appreciate improvement in overall well being of the patients, quality of life score, also family's perception and satisfaction with the new treatment addition. Most of these patients were on routine conservative treatment over average one year, they were receiving treatment under gastroenterologist as per liver cirrhosis management guidelines, these patients were having progressively worsening clinical course, quality of life, haematological and biochemical parameters. Now addition of the new treatment modality in the form of Darbepoetin and Pegfilgrastim improved the overall clinical profile, quality of life, laboratory parameters and subjective assessment scores. We did not include quality of life score, patient's care giver's perception of disease score, MELD (Model for end stage liver disease score) for analysis and comparison. Five individual factors which are noted and scored in Child's stage classification were also analyzed as per protocol, and every individual parameter except hepatic encephalopathy statistically improved. Hepatic encephalopathy is a subjective parameter with significant overlap in grade 2 and some grade 3 patients. Ascites score is also subjective but score one to three has been very well described in Child's Pugh scoring system. Improvement in albumin value was marginally significant. International normalized ratio (INR) is a very important parameter for cirrhosis prognostication in different scoring system, INR improved significantly and INR improvement was correlating with improvement in other clinical and laboratory parameters. All the haematological parameters improved significantly, platelet count is very important marker and parameter for cirrhosis staging assessment in different liver disease models, there was statistically significant improvement in platelet count, possibly it also lead to decreased incidence of gastrointestinal bleed, mucosal bleed, intracranial bleed and no patient in our study reported bleed of any kind during follow up period, there was no mortality reported during study period, three patients were lost to follow up during study, they are not included in analysis, one of them improved significantly after initial injection and did not turn up during study period, other two possibly succumbed to illness, or went to another centre, may be due to financial reason they did not turn up, it is very common happening in India, we tried but could not contact any family member due to remote location.

Limitations of the study were small number of study cohort, nonrandomized single centre study design. We will be continuing with the study, we will be collecting larger data and will compare our treatment arm patients with traditional treatment arm patients, as it was first study using only long acting erythropoietin and pegylated Pegfilgrastim in all the patients, other reports have mostly used only regular short acting Erythropoietin, regular short acting filgrastim and Darbepoetin. In future we will be publishing larger data.

In a prospective study conducted at a tertiary care centre at New Delhi for the treatment of de-compensated cirrhosis patients 3, all the study subjects were randomly assigned to two groups, one group given subcutaneous G-CSF (5µg/kg/d) for 5days and then every third day (12 total doses), along with subcutaneous Darbepoetin α(40mcg/wk) for 4weeks (GDP group, n=29) or only placebos (control group, n=26). A higher proportion of patients in the GDP group than controls survived until 12months (68.6% vs 26.9%; P=.003). At 12months, Child Turcotte Pugh scores were reduced by 48.6% in the GDP group and 39.1% in the control group, from baseline (P=.001); Model for End Stage Liver Disease scores were reduced by 40.4% and 33%, respectively (P=.03). The need for large-volume paracentesis was significantly reduced in GDP group, compared with controls (P<.05). A lower proportion of patients in the GDP group developed septic shock (6.9%) during follow-up compared with controls (38.5%; P=.005). Our Data is smaller compared to Delhi study, follow up is 3months only, but results are significantly similar, we used Pegylated Granulocyte colony stimulating factor and Darbepoetin, which to in higher dose 60 mcg and 200mg respectively, with more enhanced effect and benefits. Gradually we will be collecting one year follow up data and larger number of cases will be enrolled. We could not compare our results to other studies as there are very few publications on this particular topic, and our study is first time use of Pegylated Granulocyte colony stimulating factor and Darbepoetin in de-compensated liver cirrhosis patients.

## Conclusion

Study suggests that Darbepoetin and Pegfilgrastim is highly effective in improving International normalized ratio, ascites and Child score of the patients with de-compensated liver cirrhosis.

## Acknowledgements

None.

## Conflict of interest

Author declares that there is no conflict of interest.

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