

Association of Hemoglobin Variability with Mortality in Dialysis Patients in Tertiary Hospital Nepal

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ABSTRACT

Background: Rising number of End Stage Renal Disease patients is a great economic burden because of its high cost and lifelong treatment need. Target hemoglobin in dialysis patients is maintained through iron supplement, Erythropoietin stimulating agents, Blood products transfusions and treatment of other correctable causes. Large Hemoglobin fluctuation in such patients is related to decreased survival. The aim of this study was to relate hemoglobin variability with mortality in dialysis patients.

Methods: This is a cross sectional observational study carried out in 104 patients undergoing dialysis for a duration of one year from March 2019 to February 2020. Area Under Curve (AUC) method was used to calculate hemoglobin variability. Hb data were collected using Hospital based software.

Results: Mean age of study population was 50.15±14.1 years and 68.14% were male. Calculated hemoglobin variability was more in <15T (patients receiving less than fifteen blood transfusions per year) than >15T (patients receiving more than fifteen blood transfusions per year) group. Death to survival ratio was 0.73 in <15T and 0.41 in >15T.

Conclusion: This study showed that lesser the hemoglobin variability, better the survival in ESRD population receiving maintenance hemodialysis.

Keywords: anemia; dialysis; renal failure; mortality.

INTRODUCTION

The prevalence of chronic kidney disease (CKD) ranges from 8–16%.^{1,2} Various studies in Nepal showed the prevalence of CKD from 6- 10.2 %.³⁻⁶ Poor quality of life,⁷ premature death⁸ and high cost of treatment make it a global health problem. Cardiovascular diseases, Cancer, and infections are major causes of mortality.⁹⁻¹¹ Anemia is a major sign in CKD. Hemoglobin <13g/dL in male and <12g/dL in female is labeled anemia.¹² Mean hemoglobin is 8.23 g/dL in ESRD patient.¹³ Various studies were done for correlating hemoglobin and its variability with mortality in ESRD. Studies done in US and Japan indicated hemoglobin variability as an independent predictor of mortality^{14,15} however, similar study in Europe could not verify it.¹⁶ Recent systematic review

and meta-analysis found an association between hemoglobin variability and mortality in patients receiving hemodialysis.¹⁷ We aimed to establish significance of hemoglobin variability with mortality in dialysis patients of central Nepal.

METHODS

It's a single centered, prospective observational study done in Central Level governmental referral hospital in Nepal for a duration of one year from march 2019 to February 2020. Written Informed consent was taken from each patient prior to enrollment. Blood samples were collected prior to dialysis session. Hb was measured using Mnemonic M-series M32B Analyzer by Haemoglobinocyanide method in alternate month. Dialyzer machine of FRESENIOS

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MEDILAB CARE model 4008S, with ultra-filtration resolution of 1mL/h (Accuracy= $\pm 1\%$), temperature 35°C-39°C, blood pump rate of 250-300mL/min with heparin pump of 10mL/h, was used. Dialysis was done twice a week, four hours each session. Hb data were collected using Hospital based software. Demographics, number of Blood transfusions and health related events (Death, Survival, drop out, Referral for renal Transplant) were recorded using subject's medical record sheet. Patients of all ages and sex under maintenance hemodialysis were included. All were on oral Iron (Ferrous ascorbate equivalent to 100mg of elemental Iron, once a day). Seropositive cases (HCV/HIV/HBV), patients taking Parenteral iron and ESAs (Erythropoietin Stimulating Agents) were excluded from this study. The target HB level was set to 9-10g/dL. Being inconsistent, absolute hemoglobin level is unreliable in dialysis patients. Hence a well validated AUC (Area under the Curve) method was applied to cover Hb level along with the days of observation.¹⁸ A curve was made between Hb level and days of observation to calculate Area Under the curve of Hb. days using Trapezoidal Method as

$$\sum_{1M}^{11M} (a + b)/2 \times (d_2 - d_1)$$

Where, a= 1st Hemoglobin reading
b= Next Hemoglobin reading
 $d_2 - d_1$ = difference in days of successive observation
General statistical tools (Correlation study, Mean \pm SD,

RESULTS

Percentages, Ratio) were used using Software SPSS version 17.0 and MS excel 2019.

RESULTS

Out of 104 patients, most of the patients were in the age group 41 to 60 years group and 68.14% Male (Table 1). Represents Hb Variability over the period of one year, the strip in Y-axis represents the target Hb range. The term Hemoglobin variability is interchangeably used with AUC (mg/dL. Days). Mean Hemoglobin level was 11.7 gm/dL (Figure 1). Figure 2 revealed that, Hemoglobin variability value

Table 1. Age group distribution with gender.

Mean \pm SD=50.15 \pm 14.11	Gender	
	M (%)	F (%)
Age group (Years)		
11-20	2.77	0.96
21-30	2.88	3.85
31-40	5.77	5.77
41-50	19.23	6.73
51-60	20.19	8.65
61-70	14.42	4.81
71-80	2.88	0.96

representing target Hb level 9-10g/dL for 60 days interval is 2700-3000 g/dLdays. Our mean value was 2532.35 \pm 372.62 g/dLdays which is below the lower

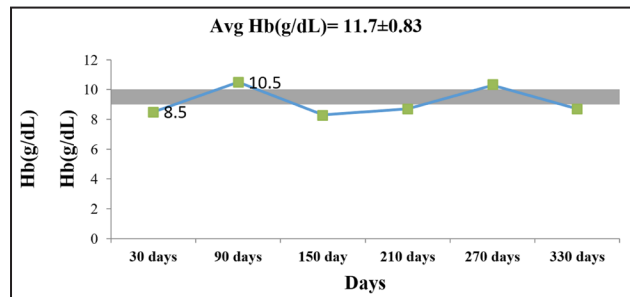


Figure 1. Hb Variability over the period of one year.

limit of target value range. This suggests that most patients were anemic. The cluster representing less than 15 transfusions suggests more variability than that for more than 15 transfusions ($p < 0.001$, $r = 0.41$). This result signifies more number of transfusions required for getting target Hb range and less variability as well. Table 2 showed that mortality occurred in 36.5% of the patients <15 transfusions while only 1% people died in those getting > 15 transfusions per year. The death to survival ratio in <15T is 0.88 while

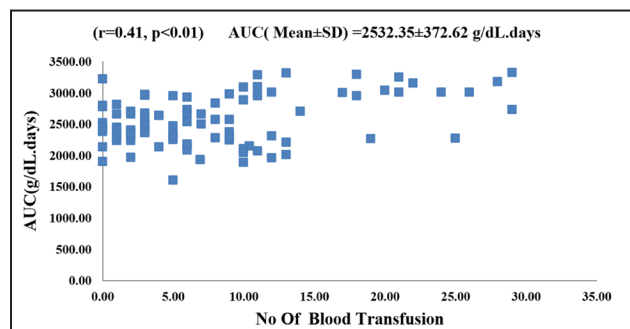


Figure 2. Scatter plot representing AUC (g/dL) days against no. of blood transfusions.

that for > 15T is 0.08. This signifies that, there is

Health Related events	No of Blood Transfusions	
	Less than 15 times (%)	More than 15 times (%)
Death	36.5	1
Referred	2.9	0
Drop out	2.9	0
Survival	41.3	12.5
Referral for Renal Transplant	2.9	0

eleven times more chance of getting mortality in < 15T group than other one. Lesser the numbers of transfusions more was the HB variability. In below 15T group, average hemoglobin variability was 2272.7 ± 227.80 (g/dL.days). In above 15T group, average hemoglobin variability was 2210.5 ± 187.2 (g/dL. days). The standard deviation value shows more variability in below 15T group with a factor of 1.21.

Hemodialysis program in 2016 after which, establishment of many dialysis centers and trained health care providers decentralized this facility.⁶ Concurrent Phase wise introduction of social Health insurance scheme helped in decreasing out of pocket expenditure in medication.⁵ Despite the investment, the outcome in dialysis patients is not promising. Inadequate dialysis and lack of standard treatment protocol could be reason behind this. Improper management of anemia is linked in many studies with poor outcome. In this study we found more than fifteen times blood transfused to maintain Hb level above 9g/dL. In contrast, those getting transfusions of less than 15 times per year were unable to maintain target Hb. Less hemoglobin variability was observed in those maintaining target Hb through multiple transfusions. Better survival was observed in those with less hemoglobin variability ($p < 0.01$; $r = 0.41$). Our result was similar to the study carried by Yang W, Israni RK et al and against the result of study carried by Eckardt

No. Of Blood Transfusions	Above 15 times	Below 15 Times	Factor
Hb Variability (Avg AUC, g/dL. days)	2210.5	2272.7	1.02
STDEV	187.2	227.8	1.21
Max	2562	2986	
Min	1785	1768	
Max-min	777^a	1218^b	(b/a) = 1.56
No of Death	1	38	
No of Survival	13	43	
Death/Survival	0.08ⁱ	0.88ⁱⁱ	
Factor	(ii/i) =11		

The minimum values for AUC calculated are similar for both groups (1785 g/dL. Days & 1768g/dL. days) but the maximum values differed significantly (2986 versus 2562gm/dL. days). This further verifies that, Hb variability is 1.56 times more in < 15T group than > 15 T group. Survival ratio in <15 transfusion and > 15 transfusion group were 0.08 and 0.88 respectively.

DISCUSSION

Government of Nepal introduced life time free

et al. in Europe.¹⁵ The mean age of dialysis population and sex ratio (M:F) was 50.15 ± 14.11 yr and 2.14, Similar to a national study done by Sigdel M et al in Kathmandu.¹³ Mean Hemoglobin was 11.7 ± 0.83 gm and maximum numbers of patients were in age group 51 to 60 yrs predominantly male 20.19%. As in other studies Male preference in health seeking behavior, hypertension, Diabetes, Smoking, alcohol consumption could be linked to more male patients in dialysis. Other reason could be inclusion of migrant

workers from gulf.¹⁹ Though mean Hb was above target, majority of patients in our study were anemic as in the study^{20, 21} done in Nepal medical college, where 85% patients were anemic. There were studies relating more hemoglobin fluctuations in patients receiving ESAs.²² Exclusion of patients receiving parenteral iron and ESAs was thus limitation of the study. Further, we have included patients aged less than 15 years too and transfusion was carried out with both whole blood and packed red cells whichever was available.

CONCLUSION

Our study revealed that increased hemoglobin

variability in ESRD patients on hemodialysis was associated with high mortality. However nationwide multicenter involving both private and governmental institutions studies are required to further generalize the findings.

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