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Evaluation Of Erythropoiesis After Renal Transplantation, A Prospective Observational Study

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ABSTRACT
BACKGROUND *Anaemia as defined by World Health Organization (WHO), American Society of Transplantation & Kidney Disease Improving Global Outcome (KDIGO) criteria is haemoglobin (Hb) ≤12 g/dL for women and ≤ 13g/dL for men[1]. Prevalence of post transplantation anaemia (PTA) ranges from 20 to 38.6 %.[2] Till date there is no data on PTA in the Indian population. This study was aimed at gaining insight in the pattern of normalization of erythropoeitic activity after Renal Transplantation (RTx), detection of prevalence of anaemia & polycythemia during the study period & to investigate any associated risk factors.*
Materials and Methods: *Collectively 100 patients were included, who met the eligibility criteria and gave written consent during the study period of one year. Patients were investigated for hematopoietic & ferrokinetic parameters in the following schedule: Pre RTx, 1, 3, 6 & 12 months of post RTx. We defined PTA as hemoglobin (Hb) ≤12 g/dL for women and ≤13 g/dL for men & post-transplant polycythemia (PTP) defined as either Hct >51 or Hb>17. All experimental protocols were approved by an institutional ethical committee, along with that informed consent statement under the ethics approval was appropriately taken.*
RESULTS: *Prevalence of PTA & Polycythemia was 7% & 15% respectively. Haemoglobin showed slow & steady increase, but Serum Erythropoietin (S.Epo) had biphasic peaks, one at 1 & other at 12 months respectively. Serum Ferritin levels rapidly declined soon after RTx & showed lowest levels at 12 months.*
CONCLUSIONS: *All ferrokinetic parameters were corrected after RTx but the sequence of correction & rate of correction were different. This study yielded strategical guide for the treatment of PTA.*
KEY WORDS: *Post Transplant Anaemia (PTA), Renal Transplantation (RTx)*

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I. INTRODUCTION

Renal transplantation is considered to be the treatment of choice for patients with CKD. A successful renal graft corrects excretory functions and endocrine functions of the kidney through the restoration of synthesis of erythropoietin & Vitamin D. It is well known that renal excretory functions are not restored completely, as majority of recipients have an estimated GFR (eGFR) of <60 ml/min/1.73 but the extent to which renal endocrine function are restored is not well understood. In the first few weeks, and even months, after transplantation, it is relatively common for kidney transplant recipients (KTR) to suffer from post-transplant anaemia (PTA) due to various reasons. Previous studies suggest that anaemia can increase the risk of cardiovascular events in patients on haemodialysis, which are reported to be the primary cause of death in KTR. Anaemia may harm the survival and quality of life in KTR through the same mechanism that affects dialysis patients[3]. Transplant European Survey on Anaemia Management (TRESAM) study, reported prevalence of PTA in nearly 37 % over five years, in more than 4,300 patients in centres across Europe. The usual pattern of PTA is a decrease in Hb levels during the first months (early onset anaemia) after Renal Transplantation (RTx), an increase approximately at 1 year, and then a second decline (late-onset anaemia) coinciding with the deterioration of graft function[4]. Several factors may determine the development of early anaemia. Data pertaining to prevalence of PTA and its current management

are inadequate and globally inapplicable, since different populations have been studied with different diagnostic criteria. Till date there is no data on PTA in the Indian population. This study was aimed at gaining insight in the pattern of normalization of erythropoeitic activity after RTx, detection of prevalence of anaemia & polycythemia during the study period & to investigate any associated risk factors, among a group of Indian KTRs under short-term(1Year) follow-up.

II. MATERIAL AND METHODS

It was a prospective observational study. Collectively 100 patients were included, who met the eligibility criteria and gave written consent during the study period of one year. All patients who underwent RTx age ≥ 18years & recipient of live Kidney donor were included in this study. Patients who had pre-existent haematological Disease, HBV, HCV Infection prior to RTx, ABO Incompatible RTx, bleeding diathesis and patient died during study period were excluded from this study. Total 137 patients, who fulfilled inclusion criteria, were enrolled in this study. Out of these 137 patients 37 candidates were excluded due to following reasons: death-7, not give valid consent- 18 & loss to follow up- 12. Out of these 100 candidates 75 were male & 25 female. Patients received induction immunosupressants with ATG (3mg/Kg in 3 divided doses, 50% at day of RTx & rest 50% divided in next two post-operative days) & Methyl Prednisolone (500mg x 2 Doses, 1st dose one day prior to RTx & 2nd dose on the day of RTx). Maintenance immunosuppressants were Tacrolimus (0.15mg/Kg in 2 divided doses), Mycophenolate Moefetil (500mg thrice daily) & Prenisolone(20mg once daily for first month of RTx then 2.5mg dose reduction per month till 5mg once daily maintenance dose reached). Prophylaxis of Cytomegalo Virus (Valganciclovir-450mg once daily for 100 days) & Pnumocystis jiroveci (Cotrimoxazole 480mg once daily for 12 months) were started. Patients were investigated for hematopoietic (Hb, S.Epo) & ferrokinetic(T.Iron, TIBC, Transferrin Saturation & S.Ferritin) , renal (S.Cr, urine R/E & C/S, USG Graft±RBx) & specialised (Bone Marrow Aspiration, JAK-2 Mutation study if required) parameters in the following schedule: Pre RTx, 1, 3, 6 & 12 months of post RTx. For estimation of above mentioned hematological & bio-chemical parameters, standard laboratory methods were used. All methods were carried out in accordance with guidelines and regulations. All experimental protocols were approved by an institutional ethical committee, along with that informed consent under guidance of the ethical committee to participate this study was appropriately taken from all participants.

All continuous variables were presented as Mean±SD or Median (1st quartile, 3rd quartile) as appropriate and all qualitative data were presented as numbers and percentages. Chi-square test or Fischer's exact test was used to see the difference between the groups for qualitative variables. Repeated measure ANOVA was used to study the differences among the means of parameters at different time period and when assumption of normality was violated, nonparametric Friedman's test was used. Between the groups, variables were compared by independent t-test or Mann-Whitney U test as appropriate. Pearson's correlation coefficient was determined to see if any relationship existed between two variables. A p-value of <0.05 was considered as statistically significant. Statistical software SPSS 20.0 was used for data analysis.

III. Results

Significant increment of Hb levels was observed at each time interval of post RTx follow up. Repeated measure ANOVA was used to test variability at different time period & p-value was <0.0001. Significant increment of S.Epo, S. Iron, TIBC and TSAT levels and decrease in S. Ferritin and S.Cr at each interval of post RTx follow up. As assumption of normality for parametric tests was violated for these variables, so Friedman's test was used and p-value was <0.0001. (Table.1)

Time	Hb (g/dL)	S.Epo (mIU/mL)	S.Iron (mcg/dL)	TIBC (mcg/dL)	TSAT (%)	S.Ferritin (ng/dL)	S.Cr (mg/dL)
	Mean±SD						
Pre RTx	8.00±2.12	10.25±10.63	43.19±18.00	189.38±43.2	23.80±10.66	1312.53±981.89	10.23±3.65
1M	10.10±1.98	21.10±15.23	62.69±26.27	195.69±40.4	32.46±11.96	769.01±330.57	1.24±0.27
3M	12.02±1.71	17.27±11.72	79.21±23.76	206.79±42.9	39.16±11.08	638.19±209.05	1.22±0.37
6M	13.71±1.57	39.34±18.39	88.90±20.68	235.72±37.5	38.31±9.031	529.38±133.46	1.22±0.53
12M	15.49±2.17	52.15±19.88	110.34±14.8	252.74±40.4	44.80±8.78	444.64±82.18	1.17±0.31

Table 1: Mean ± SD of hematopoietic & ferrokinetic parameters at different time period of RTx.

Total 25 female and 75 male patients were in this study. Prevalence of anaemia at 6 months was 27 (27%). Out of these, 7 were females (28%) and 20 were males (26.7%). Prevalence of anaemia at 12 month was 7(7%). Causes of anaemia in these seven patients were two Parvovirus B19 infection associated, one each of mixed rejection, AMR, acute Pyelonephritis, possibly Drug induced & patient due to excessive menstrual blood loss. There were no cases of Polycythemia at 6 months and 15 cases at 12 months. Causes of Polycythemia were searched & it was found mostly due to unknown factors. There was no relation between S.Epo and S.Cr at 1month (r=-0.041; p-value=0.685), 3 months (r=-0.042 p-value =0.679), 6 months (r= -0.091; p-value=0.37) but there was minor relation at 12 months (r=+0.193; p-value=0.05) (Figure. 2) . Gradual increase in Hb level over due course of time was seen, which crossed normal value after 6 months. S.Iron followed very steep rise after RTx. S.Epo had two peaks, one soon after RTx at 1 month & another at 12 months, in between there was downfall at 3 months (Figure.1&3). Though TSAT increased initially after RTx but decreased later at 6 months & again rose gradually. TIBC did not alter much throughout post RTx follow up period. S.Ferritin rapidly decreased soon after RTx & reached normal value at 6 months & afterwards (Figure.4)

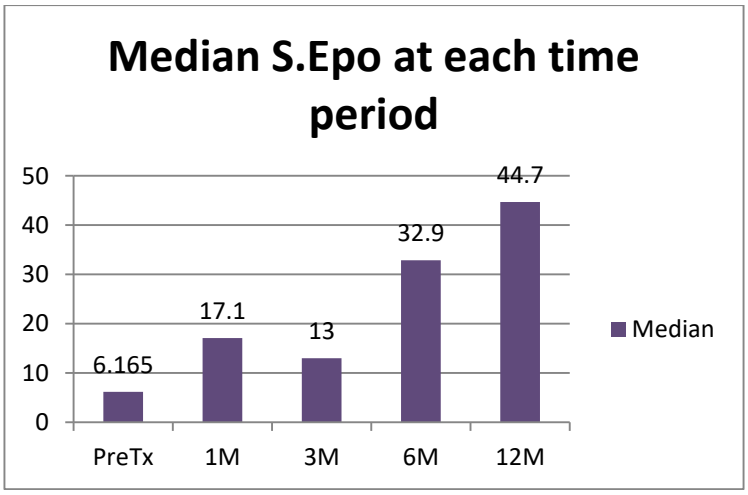

Figure.1: Medians of S.Epo (mIU/mL) at each time period

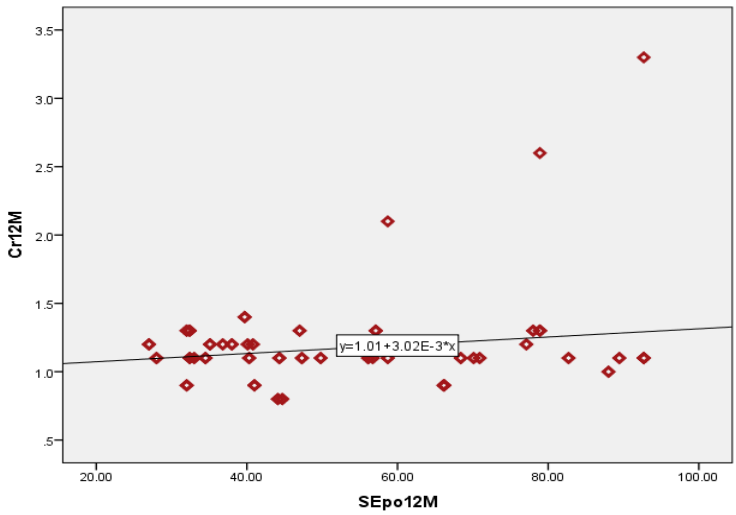

Figure.2: Correlation between S.Epo (mIU/mL) and S.Cr(mg/dL) at 12 Month. There was a minor relation at 12 months (r=+0.193; p-value=0.05).

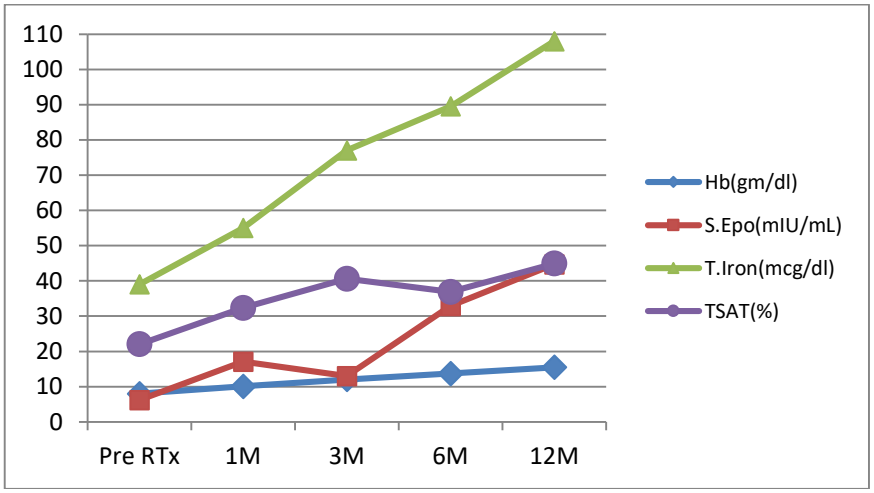

Figure.3: Mean of different parameters at different time period of RTx

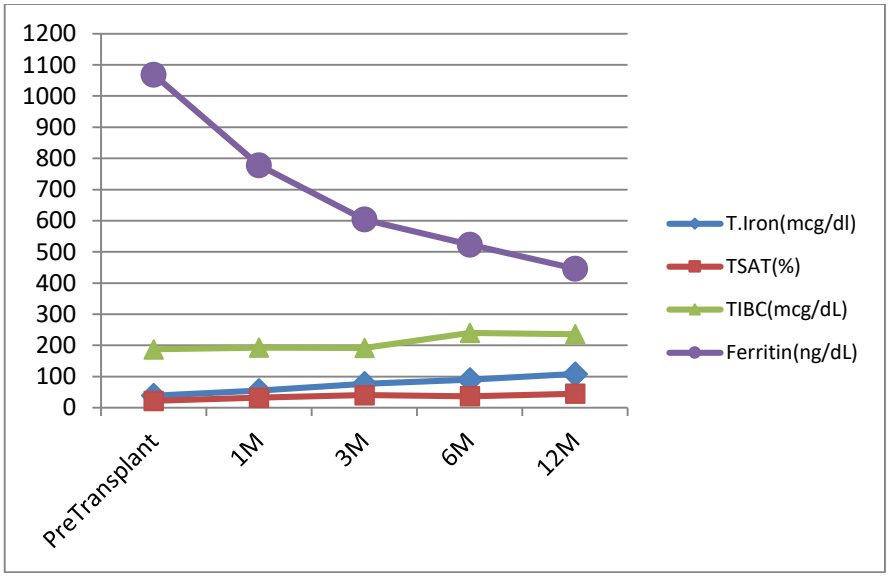

Figure.4: Mean of different parameters at different time period of RTx

IV. Discussion

Renal transplantation is considered to be the treatment of choice for patients with CKD, with excellent graft and patient survival, attributed to advances in immune suppression. However, long-term patient survival depends upon multiple factors. Filtration function of kidney restores immediately after RTx but the synthesizing function normalizes over months to years. Data depicting pattern of normalization of hematopoietic function of kidney after RTx is inadequate. Though, most patients recover from hematopoietic & ferrokinetic abnormalities with time, quite a few patients remain anaemic or polycythemic after RTx. PTA has been observed in the first few weeks and may persist for months after transplantation, whereas polycythemia has been observed months to years after transplant. There is a dearth of literature on the prevalence of PTA, changes in Ferro kinetic parameters, erythropoietic hormones and management of PTA, also these studies are not globally applicable, due to usage of different diagnostic criteria on different populations.

In this study, though 98% of patients were anemic prior to RTx, anaemia improved over months at each time interval of post RTx follow up. In the current study, anaemia was observed in 83%, 61%,27% & 7% patients at 1,3,6 & 12 months respectively. These findings corroborate with the data from the Spanish National Transplant Organization,[5] wherein among 2139 RTxs in 2007 in Spain, a very high prevalence of anaemia was observed within the first month after transplantation (75% patients), which decreased quickly within the second month, and gradually later, achieving minimum values (15% patients) between 1 and 2 years.

Though there was correction of pre RTx anemic status, but high prevalence of anaemia post RTx persisted. Various causes for PreRTx anaemia include anaemia of chronic disease, frequent blood loss during HD or sampling, nutrient deficiency (Iron, Folic acid, Vit-B12) & erythropoietin resistance due to persistent uremic

milieu[6]. In patients with well-functioning allograft, anaemia usually resolves by 3 to 6 months after transplantation[7].

S.Epo levels had biphasic peaks at 1 month & 12 months, with a dip at 3 months. The initial peak was not associated with rise of Hb levels, suggestive of relative erythropoetin resistance during this period (Figure.1&3). Erythropoietin levels start rising on posttransplant day 2 and reach a fourfold elevation for two to three weeks, after which restoration of negative feedback control occurs.[8] Relative erythropoietin deficiency in the setting of allograft dysfunction is similar to that observed with anaemia in patients with nontransplant associated CKD. Sun et al.[7] & Brown et al.[9] reported that quick production and short-lived peak of erythropoietin happens within few days of transplantation, which is insufficient to generate a meaningful increase in hemoglobin. A second, smaller but more sustained peak occurs after 28 days, which was associated with the subsequent onset of erythropoiesis and recovery of anaemia over the next two to three months[6]. In the current study, short term peak of S.Epo may have been missed before 1 month, as patients were not evaluated for the same, during the first month of post RTx. In the current study, the normal range of S.Epo was considered as (4.1-19.5)mIU/mL in adults.

In the present study there was significant improvement in S.Iron, TIBC & TSAT levels at each time interval of post RTx follow up (Table.1). TSAT values <30% were observed in 75% & 3% of patients at the time of RTx & one year after RTx, respectively. Although few authors described the stage of iron deficiency but none of them illustrated the course of Iron deficit correction over time. In addition, data pertaining to prevalence of iron deficiency has not been mentioned. In this study S.Iron had reached normal value within 1-3 month of post RTx, wherein normal range of S.Iron was considered as 55 – 160 mcg/dL in males and 40 - 155 mcg/dL in females. Previous studies have not illustrated the changes of TIBC post RTx. In the current study, TIBC attained normal value within 6-12 month of post RTx, wherein normal range of TIBC considered was 255 - 450 mcg/dL. In the present study TSAT reached normal value after 1 month of post RTx (Figure. 3 & 4). Studies describing post RTx TSAT course are unavailable. In the present study, normal values of TSAT considered were 20-50 %. Further studies are required to ascertain the course of iron deficit correction, evolution of TIBC & changes in TSAT values post RTx. In this study, Iron deficiency was found to be an important cause of anaemia at the time of RTx but not in late post RTx period.

In the present study there was significant decrease in S.Ferritin levels at each interval of post renal transplantation follow up. Teruel et al in their study on serum ferritin levels among 112 patients of post renal transplant with good graft function, observed rise in hemoglobin value with a decrease in basal serum ferritin levels, with lowest levels at the sixth month[10]. The values of serum ferritin being 54.9 (2-1,516) mcg/l vs. 109.6 (21-4,420) mcg/l, p value less than 0.001. Ferritin values subsequently increased, though basal levels were not attained. Evolution of serum ferritin after transplantation is mainly determined by the previous state of iron stores, at the time of transplantation[10]. Ferritin, an acute-phase reactant, is frequently elevated after transplantation as a result of inflammation, infection, increased iron absorption and iron overload due to multiple blood transfusions & rejection. Studies show maximum decrease in S. Ferritin at 6 months, following by increased values, though basal levels were not attained. Evolution after transplantation was mainly determined by the previous state of iron stores at the time of transplantation. The differences between high basal & low basal S.Ferritin disappeared at the 36th month of post RTx, with similar in all groups[10]. Though, the present study showed least S.Ferritin levels at 12 months post RTX, wherein normal S.Ferritin levels were considered as 23-336 ng/mL for male & 11-306 ng/mL for female.

Prevalence of anaemia at 6 months & 12 months were 27% & 7% respectively. Anaemia was slightly more common in females than males at 12 months of post RTx follow up.

Authors	location	No of Patients	Def. of Anaemia	Prevalence
Saito et al[12].	Japan	60	Hb<12.8(M), <11.5(F)	20%
Yorgin et al.[11]	USA	128	Hct<33	30% at same point of RTx, 26% at 5 year of Post RTx.
Vanreterghem et al.[2]	Europe	4263	Hb<13(M), <12(F)	38.6%(11.6% had moderate & 8.5% had severe anaemia
Current Study	India	100	Hb≤12.5	7%

Table.2: Summary of publications presenting the results of studies of anaemia following Renal Transplantation[2,11,12]

In a study done in Turkey, younger age and female gender were found to be significant risk factors for severe anaemia pre transplantation. There was a significant correlation between post transplantation Hb levels and serum creatinine levels at 12 month (p =0 .01). Recipient of female gender and longer hospital stay were significant risk factors for both anaemia and severe anaemia post transplantation.[13]

In a single-center retrospective cohort study using the Rabin Medical Center (RMC) transplantation department registry revealed that the prevalence of PTA at 6 months (early PTA) was 51.3% and at 2 years (late PTA) was 36.6%. Female sex was significantly associated with early PTA[18].

In the present study prevalence of anaemia was low (7%), in comparison with other studies (Table.2). It is difficult to explain the possible cause of this low prevalence of anaemia, though high prevalence (75%) of Iron deficiency at the time of RTx, corrected within initial months of RTx could be a cause for low prevalence. Females were more prone to develop to anaemia compared to males. This observation was similar to previous studies.

In this study, polycythemia cases at 6 months and 12 months were zero & 15 respectively, with no significant gender distribution. Prevalence of polycythemia was of the order of 10% to 15%, varying from as 2.5% to 22.2%[14,15] in previous studies. Kessler et al in a study of 81 consecutive allograft recipients noted that 22.2% of patients developing true increase in red cell mass were more frequently male[16]. Sumrani et al found true polycythemia in 8.1% (25/307) of patients. Polycythemia was much more common in males and diabetics and occurred among patients with excellent graft function[16]. In the current study, incidence of polycythemia was 15% which is similar to that of previous studies.

Current study showed no correlation between Hemoglobin and S.Cr at 1 month, 3 months & 6 months but significant negative correlation was observed at 12 months (Figure.2). In a China-based study on prevalence of PTA, hemoglobin levels were found to be associated with graft function. No correlation between anaemia and age, gender, immunosuppressive regimens or antihypertensives was observed. Binary logistic regression analysis suggested that serum creatinine and blood urea nitrogen were associated with the diagnosis of anaemia at 1 year post-transplant. At 5 years post-transplant, only serum creatinine concentrations correlated with anaemia[17]. The TRansplant European Survey on Anaemia Management (TRESAM) was a cross-sectional questionnaire- based analysis involving 72 centers and 4263 patients stated that reduced transplant function, use of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), donor age and recent infections correlate with PTA[2].

In the present study after 1 year of post RTx follow up, 7 patients were anaemic & 15 were Polycythemic. Among 7 cases of anaemia, 2 cases each were attributed to rejection and associated Parvovirus B19 infection, and one case each due to acute Pyelonephritis, Drug induced & excessive menstrual blood loss. No etiological factor for Polycythemia could be ascertained, and was found mostly due to unknown factors (JAK-2 Mutation Negative). Most studies showed that allograft function strongly correlates with anaemia. Post-transplantation anemia is significantly associated with late mortality, with a decline in graft function and with an increased incidence of graft failure.[18,19] In one recent Spanish study showed that low Hb levels in the early posttransplantation period (1 month) seem to be an independent prognostic factor for graft loss, but not for mortality in Spanish RTx patients regardless of graft function, recipient and donor characteristics, unfavourable events within the first month, and immunosuppression[20].

TRESAM showed that creatinine clearance <50 ml/min and serum creatinine >2 mg/dl correlated with anaemia[2]. Transplant recipients who experienced rejection episodes or received more than one transplant have a higher incidence of anaemia. The underlying factors causing anaemia in the setting of rejection may include suboptimal kidney function, more intensified immunosuppression, acute inflammation, or perhaps a chronic inflammatory state leading to EPO resistance. Acute rejection can lead to a rapid decrease in EPO levels that is reversible on treatment of rejection[8]. In this TRESAM study it was concluded that patients with S.Cr>2mg/dL 60.1% were considered anaemic, whereas in patients with S.Cr≤2mg/dL only 29% of patients were considered anaemic ($p<0.01$)[2]. This indicates that low S.Cr group patients are less anaemic, when compared with high. But data shows its significant relation only in first month of RTx.

V. CONCLUSION

Despite the restoration of normal filtration function of kidney in most patients with well-functioning grafts, it was observed that the erythropoetic activity restored gradually over period of one year & some patients remain either anaemic or polycythemic at one year of post RTx. All ferrokinetic parameters were corrected after RTx, but the sequence of correction & rate of correction were different. At the end of 6 months most were corrected & at the end of one year none of the patients had abnormal ferrokinetics. S.Epo levels showed bimodal peaks, maximum at 12 months, with early peak at 1 month, associated with relative Epo resistance. There was significant negative correlation between Hb & S.Cr at 12 months. Patients with S.Cr>1.3mg/dL were mostly anemic. This study yielded strategical guide for the treatment of PTA. Iron replacement should be helpful in early post RTx period[19], whereas S.Epo is inefficient, probably due to state of S.Epo resistance. Though, S.Epo may be helpful at the end of 1 year, when all ferrokinetics are normalized, especially in presence of graft dysfunction. Attempts were made to search for causes of Polycythemia, but in most cases the etiology was found to be idiopathic. The causes of anaemia comprised of rejection, infection, blood loss & drug Induced. This study is unique because PTA has not been studied prospectively and extensively in this part of the country with special emphasis on the changes in post RTx Ferrokinetic & Hematopoetic parameters.

VI. Limitations

This was a study with short study duration wherein patients were followed up one year post RTx. This duration should be extended further in subsequent studies. This study, being a single centre-based study, only the patients enrolled in one institute were included. Subsequent studies comprising of multiple populations are required. This study being an observational study, no interventional measures were taken. Upcoming studies including the effects of intervention may add to the existing knowledge in this field.

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