A Descriptive Study of Erythrocytosis Post Kidney Transplant, A Single Center Experience

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ABSTRACT:

BACKGROUND :

Post Transplant Erythrocytosis (PTE) is relatively a common complication following renal transplantation, occurs in 8 to 15 percent of renal transplant recipients ,it is mainly due to adequate production of erythropoietin by the transplanted graft and elimination of bone marrow inhibitors attending the uremic symptoms.

OBJECTIVE:

This study was conducted to know the prevalence, manifestation , and risk factors of Post Transplant Erythrocytosis (PTE).

PATIENTS AND METHODS:

This is an observational retrospective study enrolled 290 patients who underwent kidney transplantation and followed up at The Nephrology and kidney transplantation Center, Medical City Baghdad , The data used in this study were collected from the patients, their medical records and from the laboratory. The follow up period was from the third months post transplant to the end of first year. These data include (name, age, sex ,weight, etiology of chronic renal failure, duration of hemodialysis before transplantation, the use of erythropoietin stimulating agent, living kidney donor (related or unrelated), The use of basilixmab or Anti Thymocyt Globulin) at induction, the calcineurine inhibitor (cyclosporine or tacrolimus), the occurrence of acute rejection, the type of antihypertensive used post transplant .Laboratory data include ,hemoglobin level, red blood cells packed volume, serum creatinine .

RESULT :

Twenty three patients (7.9%) had erythrocytosis post kidney tranplantation with Hemoglobin level of 17.5 g/dl (17 -17.9) and PCV of 54 % (52.1 – 54.4). Only two patients (8.7 %) had cerebrovascular accident. From the non transplant related parameters, hypertension was significantly associated with PTE (P Value of 0.026). While the others (age , gender, weight , etiology of the ESRD and the duration of dialysis) showed no significant association. From the transplant related parameters, low serum creatinine (0.8-1.2mg/dl) showed significant association with PTE (P value <0.0001). Also both hypertension and the use of Beta blocker shows significant association (P value <0.05)

CONCLUSION:

Post transplant erythrocytosis occurs in about eight percent of kidney transplant recipient, it may be asymptomatic or complicated by thrombotic event, and it is associated with lower serum creatinine and hypertension.

KEYWORDS: kidney transplant , erythrocytosis.

INTRODUCTION:

Post-kidney Transplant Erythrocytosis (PTE) is one of the hematological complications in the renal transplant patients.[1]

It occurs in 8 to 15 percent of renal transplant recipients and usually affects patients with well-preserved graft function.[2]—Post-transplant Erythrocytosis is defined by most as a persistently elevated hematocrit to a level greater than 51% in renal graft recipients.[3]

Pathogenesis of PTE:

Erythropoietin is the main hematopoietic cytokine that regulates the formation of red blood cells in the process of hematopoiesis. This effect is mediated by its interaction with the EPO receptor, which is preferentially expressed in erythroid cells, but also in many non-hematopoietic cells, including vascular endothelial cells and cancer cells.[4]. With immediate graft function, erythropoietin secretion peaks within three days, reticulocytosis

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begins at one week, and correction of anemia is anticipated over three months. Thereafter erythropoietin levels decline.[5] The type of immunosuppression, the level of graft function, and the occurrence of acute rejection appear to influence the rate of correction of renal anemia and the level of hematocrit attained.[6]

Two major factors contribute to the correction of anemia after successful renal transplantation: adequate production of erythropoietin by the transplanted graft: and elimination of bone marrow inhibitors attending the uremic symptoms.[7]However, plasma EPO-levels do not seem to be a reliably measure of the contribution of EPO to the development of PTE, as levels were similar between patients with and without PTE in the study of Brox et al. [8]. Unidentified factors not related to EPO appear to contribute to PTE, supported by the finding of normal or even appropriately suppressed plasma EPO levels in patients with PTE [9]. The non- EPO factors may either enhance the sensitivity to EPO or directly promote erythropoiesis [10]. As an example, an anomaly in IGF-1 and its binding proteins-1 and 3 have been accused to induce PTE [8]. The observation, that stimulation of marrow CFU-E growth by serum from hemodialysis patients with erythrocytosis can be partially blocked by anti-IGF-I antibodies, suggests that IGF-I is physiologically active in this particular setting [11]. It has also been suggested that activation of the Angiotensin-II-receptor may enhance erythropoietin production in the graft or increase sensitivity of red cell precursors to erythropoietin [12] The rennin–angiotensin system can induce the hypoxia-inducible factor and promotes the production of erythropoietin and PTE [13]. A role for renal artery stenosis and subsequent renal ischemia leading to increased erythropoietin production has been postulated [14].

Risk factors for PTE include the presence of native kidneys, male gender, excellent graft function and absence of rejection episodes, high hemoglobin baseline before transplant and hypertension [15] . Smoking and diabetes have been shown to be a risk factor for PTE in some but not all studies. Other suggested risk factors include polycystic kidney disease and glomerulonephritis as a cause of end stage renal disease. Transplant renal artery stenosis has not been consistently shown to be a risk factor. Serum soluble stem cell factors have been shown to correlate with both hematocrit value and with the observed and expected EPO values in renal transplant recipient with PTE. [16]

Erythrocytosis can increase plasma viscosity and may cause thromboembolic events. Wickre et al. reported an increase in thromboembolic events (18.9%) in patients with PTE, despite therapeutic phlebotomy, when compared to non-PTE patients (0%) [17] Others, found that thrombotic events are rare [18] or did not find an association between PTE and increases of thromboembolisms. [19]

Treatment of PTE;-

The treatment goal in patients with PTE is to lower Hb-level below 17.5 g/dl in normotensive patients .As PTE can have a relapsing course, it is suggested that PTE therapy should be pursued indefinitely. [3] Treatment is generally recommended for hemoglobin level exceeding 17 to 18 g/dl or a hematocrit level over 51% to 52% because the associated risk of thromboembolic complications , hypertension or headaches .

Treatment with ACE inhibitors or ARBs is often sufficient and becoming the standard form of therapyFrequent phlebotomy may occasionally be necessary.[20]. Native kidney nephrectomy [21] ,and theophylline [22] are also considered in the management of PTE.[23]Inhibitors of the renin-angiotensin-system ACEi and ARBs decrease Hb-levels in kidney allograft recipients by 0.2–0.3 g/dl [24].The effect of ACEi may be mediated by Ac-SDKP (goralatide), a tetrapeptide that inhibits erythropoiesis [25].Theophylline acts as an adenosine antagonist. Adenosine facilitates the release and perhaps the bone marrow response to EPO. The effectiveness of theophylline cannot be predicted as reliable as for ACEi [26].

THE AIM OF THE STUDY:

The aim of the study is to know the prevalence , manifestation , and the risk factors of Post Transplant Erythrocytosis (PTE).

PATIENTS AND METHODS:

This is retrospective study conducted at The Nephrology and Renal Transplantation Center, Medical City, Baghdad , Iraq. From the 1st of January 2014 – 31st of December 2016.

Definition:

Post transplant erythrocytosis (PTE) is defined as persistently elevated hemoglobin and hematocrit levels that occur following renal transplantation and persist for more than six months in the absence of thrombocytosis, leukocytosis, or another potential cause of erythrocytosis .[3] The threshold hematocrit used to define PTE is variable and ranges between 51 to 54 percent; most clinicians use 51 percent (corresponding to a hemoglobin concentration of approximately 17 g/dL.[12]

Patient characteristics:

Two hundreds and ninety patients who underwent kidney transplantation and followed up at The Nephrology and Renal transplantation Center, Medical City Baghdad , Iraq, were involved in this study.

Inclusion criteria:

we include the patients with the following criteria;-

- Post kidney transplantation period from third to the twelfth month.
- Non smoker
- No clinical , laboratory or ultra sonic finding of polycythemia rubra vera
- All the patient did not receive ESA post transplant

The data used in this study were collected from the patients, their medical records and from the laboratory

from the third months post transplant to the end of first year. These data include (name, age, sex ,weight, etiology of chronic renal failure, duration of hemodialysis before transplantation, the use of erythropoietin stimulating agent, living kidney donor (related or unrelated),the use of basilixmab or ATG (Anti Thymocyt Globulin) at induction, the calcineurine inhibitor (cyclosporine or tacrolimus), the occurrence of acute rejection, the type of antihypertensive used post transplant (Beta blocker , calcium channel blocker , angiotensin converting enzyme inhibitors or angiotensin receptor blockers). Laboratory data include;-

1,Complete Blood Count (hemoglobin level ,packed cell volume, red blood cells indices, white blood cells total and differential counts, platelets count and blood film.

2.Serum creatinine .

The average of multiple readings of hemoglobin level, packed cell volume and s.creatinine were taken , Clinical data include the symptoms of headache , dizziness any thrombotic events and the management used for Erythrocytosis (angiotensin

converting enzyme inhibitors , angiotensin receptor blockers or phlebotomy).

Statistical Analysis:

Continuous data presented as mean and standard deviation if it follows normal distribution, while if they did not follow normal distribution there median and interquartile range (25% - 75%) will be used, discrete variables presented using their number and percentage. To analyze the difference between two mean independent t used was used (for normally distributed data), Mann Whitney U test used to analyze the statistical significance between two median (none parametric variables). Chi square test used to analyze the difference in distribution of discrete variables.Univariate logistic regression analysis used to calculate the odd ratio and its confidence interval for each possible risk factor for erythrocytosis, than multiple logistic regressions used to test if these significant risk factors are independent risk factors. All data analyzed using SPSS version 20 software package, level of significance was 0.05 so if p value <0.05 will be significance

RESULTS:

Table 1 shows that from a total of 290 patients, 206 (71%) were males and 84(29%) were females. The average age was 35.7years. Hypertension was the most common etiology of end stage renal disease in those patients who underwent kidney transplantation (125, 43.1 %). The average duration of dialysis was 6 months. 168 (57.9%) of the kidney donors were unrelated ones . Acute rejection occurred in 67 (23.1%) of the patients.

Table 1:Characteristics of the patients involved in the study

Number			290
Age (years)			35.7 ± 12.1
Weight (kg)			63.5 ± 17.0
Gender	Male		206 (71%)
	Female		84 (29%)
Etiology of the chronic kidney disease	Hypertension		125 (43.1 %)
	Unknown		85 (29.3 %)
	Glomerulonephritis		47 (16.2 %)
	Diabetes mellitus		21 (7.2 %)
	Others	Total	12 (4.1 %)
		Alport syndrome	4 (1.5%)
		Adult Polycystic Kidney Disease	3 (1.0%)
		SystemicLupus Erytematosus	3 (1.0%)
		IgA nephropathy	1 (0.3%)
		Vesico-uretric reflux	1 (0.3%)
Duration of dialysis (months)			6 (2 – 8)
Donor	Unrelated		168 (57.9%)
	Related		122 (42.1%)
Induction therapy	Baciliximab		278 (95.9%)
	ATG (Antithymocyte globulin)		12 (4.1%)
CNI (Calcineurine inhibitor)	Tacrolimus		74 (25.5%)
	Ciclosporin		216 (74.5%)
S.Creatinine mg/dl			1.3 (0.8 – 4.4)
Acute rejection	Yes		67 (23.1%)
	No		223 (76.9%)

Twenty three patients (7.9%) from 290 ones had erythrocytosis as shown in figure No.1

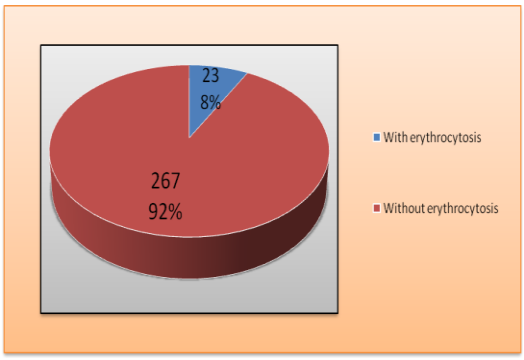

Figure 1: Prevalence of erythrocytosis in post kidney transplant patients.

In those patients with erythrocytosis post kidney transplant , the average hemoglobin was 17.5 g/dl (17 -17.9) and the average PCV was 54 % (52.1 – 54.4) as shown n table 2.

Table 2: Prevalence of erythrocytosis post kidney transplant with hemoglobin and PCV values

	No (%)	g/dl Hb	PCV %
With erythrocytosis	23 (7.9%)	17.5 (17 -17.9)	54 (52.1 – 54.4)
Without erythrocytosis	267 (92.1%)	12 (11 – 13)	36 (33 – 40)

Table 3: Clinical manifestations of erythrocytosis post kidney transplantation

		No. (%)
Manifestations	Headache	7 (30.4 %)
	Dizziness	4 (17.4 %)
	Cerebrovascular accident	2 (8.7 %)
	None	10 (43.5 %)
Managements	ACEI or ARBs	23 (100 %)
	Vensetion	8 (38 %)

From the non transplant related parameters, hypertension was significantly associated with PTE (P value 0.026) . While the other parameters (age , gender, weight , etiology of the ESRD and the duration of dialysis) showed no significant association (P value > 0.05) as shown in table 4.

Table 4: Non transplant related parameters of patients with & without erythrocytosis post kidney transplant.

		Erythrocytosis		P value
		With	Without	
Number		23 (7.9%)	267 (92.1%)	-
Age (years)		36.8 ± 11.1	35.6 ± 12.2	0.657[a]
Gender	Male	20 (87%)	186 (69.7%)	0.079[b]
	Female	3 (13%)	81 (30.3%)	
Weight (kg)		68.6 ± 15.5	63.0 ± 17.1	0.135 [a]
Etiology	Hypertension	15 (65.2%)	110 (41.2%)	0.026 [b]
	Diabetes mellitus	3 (13.0%)	18 (6.7%)	0.263 [b]
	Glomerulonephritis	2 (8.7%)	45 (16.9%)	0.308 [b]
	Unknown	3 (13.0%)	82 (30.7%)	0.074 [b]
	Others	0	12 (4.5%)	0.299 [b]
Duration of dialysis (months)		6 (2 – 8)	6 (2 – 8)	0.745 [c]
[a] Independent t test, [b] chi square, [c] Mann Whitney U test				

From the transplant related parameters, lower serum creatinine (0.8-1.3 mg/dl) showed significant association with the erythrocytosis post kidney transplant with P value <0.001 . Also both hypertension and the use Beta blockers had significant association with P value and of 0.026 and 0.021 respectively as shown in table 5.

Table 5: Transplant related parameters of patients with/without erythrocytosis post kidney transplant.

			Erythrocytosis		P value
			With	Without	
Number			23 (7.9%)	267 (92.1%)	-
Donor	Unrelated		13 (56.5%)	155 (58.1%)	0.887[a]
	Related		10 (43.5%)	112 (41.9%)	
Induction	Baciliximab		22 (95.7%)	256 (95.9%)	0.958 [a]
	ATG (Antithymocyte globulin)		1 (4.3)	11 (4.1%)	
CNI (Calcineurine inhibitor)	Tacrolimus		5 (21.7%)	69 (25.8%)	0.665 [a]
	Ciclosporin		18 (78.3%)	198 (74.2%)	
Creatinine (mg/dl)			1.1 (0.8-1.3)	1.3 (0.9-4.4)	<0.001[b]
Acute rejection	Yes	67	2 (3 %)	65 (97%)	0.088 [a]
	No	223	21 (9.4%)	202 (90.6%)	
Hypertension	Yes	229	22 (9.6%)	207 (90.4%)	0.026
	No	61	1 (1.2%)	81 (98.8%)	
Anti-hypertensive	ACEI or ARBs		2 (11.1%)	16 (88.9%)	0.606[a]
	Beta blocker		7 (16.8 %)	59 (83.2%)	0.021[a]
	CCB		10 (7.8 %)	118 (92.2%)	0.460[a]
	ACEI+BB		1 (33.3%)	2 (66.7%)	0.220[b]
	BB+CCB		2 (22.2%)	7 (87.8%)	0.107[a]

[a] Chi square, [b] Mann Whitney U test,

Possible Risk factors associated with Erythrocytosis

Hypertension and its medication appeared to be have significant prediction for the development of erythrocytosis. Hypertension (in unadjusted analysis) appear to predict erythrocytosis by 2.676 folds increase in the risk, the use of beta blocker also increase risk by 2.712 folds, while no treatment appear to have protective effect, as illustrated in table 6 and figure 2.

Some other variables in this univariate logistic regression analysis appears to provide either protective or harmful effect but did not reach the statistical significance; so multivariate regression analysis (using backward elimination methods) to choose the best risk factors that explain most of the variability is done as illustrated in table 6 .

Table 6: Possible risk factors to predict Erythrocytosis.

P value	95%CI	OR	
0.656	0.973 – 1.044	1.008	Age
0.092	0.839 – 10.045	2.903	Gender (male)
0.136	0.994 – 1.043	1.018	Weight
0.831	0.87 – 1.19	1.017	Duration of dialysis
0.887	0.398 – 2.219	0.939	Donor (unrelated)
0.958	0.13 – 8.578	1.058	Immunomodulators (Baciliximab vs ATG)
0.665	0.449 – 3.507	1.255	Cytotoxic drug (Ciclosporin vs Tacrolimus)
0.106	0.771 – 14.799	3.379	Acute rejection
0.002	0.012 – 0.363	0.065	Creatinine
0.031	1.097 – 6.53	2.676	Hypertension
0.273	0.563 – 7.647	2.075	DM
0.319	0.106 – 2.075	0.47	GN
0.338	0.098 – 1.171	0.338	Unknown
0.608	0.322 – 6.941	1.494	ACEI/ARB
0.025	1.132 – 6.496	2.712	BB
0.462	0.587 – 3.233	1.378	CCB
0.028	0.014 – 0.788	0.104	No treatment
0.149	0.525 – 69.066	6.023	ACEI/BB combination
0.129	0.691 – 18.112	3.537	BB/CCB combination
Univariate binary regression analysis			

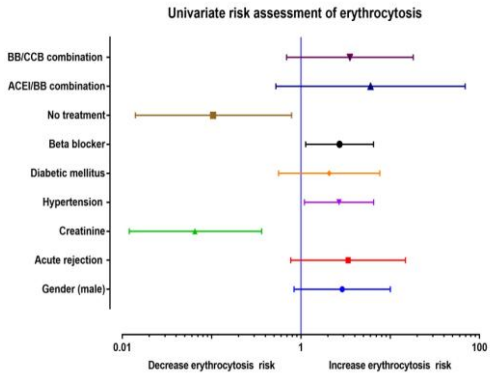

Figure 2: Forest plot of different risk factors for erythrocytosis post kidney transplantation (Universal risk assessment.)

Optimal module of risk of predictors of erythrocytosis

Creatinine maintained in this module a significant protective effect mean he exert his effect independently of the effect of others, despite that male gender did not reach the statistical significance (p value =0.051) however it exert 3.7 folds increase in erythrocytosis which give us an idea of possible association between male and erythrocytosis.

Hypertension and its medication: Beta blockers, CCB, combination of ACEI/BB all appears to be significant risk factors for erythrocytosis (independent). Overall, this module is good and significant for predict hypertension since the constant is significance. Table 7and figure 3

Table 7: Multivariate analysis of possible risk factors to predict Erythrocytosis.

P value	95%CI	Adjusted OR	Variables
0.051	0.996 - 13.755	3.702	Gender (male)
<0.001	0.007 - 0.229	0.039	Creatinine
0.047	1.015 - 7.280	2.719	HTN
0.005	1.765 - 23.765	6.477	BB
0.021	1.260 - 16.54	4.565	CCB
0.017	2.014 - 1374.56	52.621	ACEI/BB combination
0.001	-	-	Constant
Multiple binary logistic regression (backward selection method)			

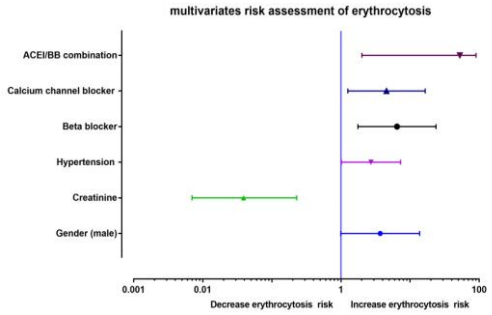

Figure 3: Forest plot of different risk factors for erythrocytosis post kidney transplantation (Multivariable risk assessment.)

DISCUSSION:

The prevalence of erythrocytosis post kidney transplant in this study was (7.9%) with an average hemoglobin level of 17.5 g/dl (17 - 17.9) and PCV of 54 % (52.1 – 54.4) In comparism with other studies done by Kiberd ,Vlahakos ,.Augustine. [2] PTE occurs in 8 to 15 percent of renal transplant recipients; and few studies, as those done by Einollahi etal and Friman etal,have reported incidences as high as 22 percent [27,28] .This difference in reported prevalence is due in part to the variably defined hematocrit thresholds used and the inclusion of transitory erythrocytosis (ie, persisting for less than six months) Ten patients (43.5 %) of those who developed erythrocytosis , were asymptomatic , and were noticed only by reviewing investigation .Those who were symptomatic, few patients had headache, dizziness, and only two patients (8.7%) had cerebrovascular accident. This is because erythrocytosis can increase plasma viscosity which leads to thromboembolic events. Wickre et al. [17] reported a higher incidence of thromboembolic events (18.9%) in patients with PTE than in our study. This low incidence in our study may be due to close follow up of our patients and the earlier use of ACE inhibitor. Other s, however, did not find an association between PTE and increases of thromboembolisms. [7] All those patients were given an ACEI (lisinopril) or ARBs (valsartan) while phlebotomy was done only for eight (38 %) patients.

From the non transplant related parameters, hypertension was significantly associated with PTE (P 0.026). Hypertension is probably associated with generalized powerful vasoconstrictor activity affect the whole circulation including the renal circulation, leading to increase resistant to renal blood flow and thereby increase erythropoietin secretion. [29] The other non transplant realted parameters (age , gender, weight , etiology of the ESRD and the duration of dialysis) showed no significant association with the incidence of erythrocytosis post kidney transplant with P value < 0.05. This is because these factors have no effect on erythropoietin production . We have to mention

here that a limited number, only three patients (1.0%) with Adult Polycystic Kidney Disease involved in the study .

From the transplant related parameters, lower serum creatinine (0.8-1.2mg/dl) post kidney transplantation showed significant association (P value < 0.001) with the prevalence of erythrocytosis . This could be explained by the increase of erythropoietin secretion from the renal allograft and the regain of bone marrow activity after the clearance of uremic toxins and their suppressive effect on bone marrow activity . Also both hypertension and the use Beta blockers had significant association with P value and of 0.026 and 0.021 respectively.

While the other transplant related factors (donor-related or unrelated , induction treatment and the type of CNI (cyclosporine or tacrolimu) showed no significant association with PTE.

Possible risk factors associated with erythrocytosis:-Hypertension and its medication appeared to have significant prediction for the development of erythrocytosis. Hypertension (in unadjusted analysis) appear to predict erythrocytosis by 2.676 folds increase in the risk, The use of beta blocker also increase risk by 2.712 folds, while no treatment appear to have protective effect,

Some other variables in this univariate logistic regression analysis appears to provide either protective or harmful effect but did not reach the statistical significance; so multivariate regression analysis (using backward elimination methods) to choose the best risk factors .

Optimal module of risk of predictors of erythrocytosis:- Creatinine maintained in this module a significant protective effect mean it exert its effect independently of the effect of others, despite that male gender did not reach the statistical significance (p value =0.051) however it exerts 3.7 folds increase in erythrocytosis which give us an idea of possible association between male and erythrocytosis, Androgens enhance sensitivity of primitive erythrocytes to EPO, activating increased erythropoiesis in male patients[30] . Hypertension and its medication: Beta blockers, CCB, combination of ACEI/BB all appears to be significant risk factors for erythrocytosis (independent). Overall, this module is good and significant to predict hypertension since the constant is significance.

CONCLUSION :

Post kidney transplant erythrocytosis occurs in about 8% of renal allograft recipient, it may be asymptomatic, mild symptoms or complicated by thrombotic disease and it is associated with lower s. creatinine and with hypertension.

RECOMMENDATIONS:- It is advisable to use ACE inhibitor to control post transplant hypertension with erythrocytosis.

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