EVALUATION OF ANEMIA IN RENAL TRANSPLANT PATIENTS

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ABSTRACT

Background

Post-renal transplant anaemia is a common complication among renal transplant patients. Graft dysfunction, medications, and IDA are the most common causes of PTA.

Objectives

To investigate further the prevalence of anaemia after kidney transplantation in Sulaimani city, determine the risk factors and the association of different socio-demographic characteristics with PTA, and identify the essential causes of anaemia

Patients and Methods

A cross-sectional descriptive study was conducted on two hundred renal transplant patients who visited Shar-hospital in Sulaimani city for their regular follow up between January/ 2020-January/ 2021.

Results

Among the total 200 patients involved in the study, 63% were males, 37% were females, mean age was 45.32±9.28. It demonstrated that PTA was remarkably high (40%). Iron deficiency anaemia is the most common cause of PTA 28.75%, especially in 1st six months after renal transplantation; GFR decline for any reason (rejection, ATN, viral infection) is significantly associated with anaemia; the lower the GFR, the higher number of anaemic patients (p=0.000).

Conclusion

Our findings showed that anaemia is widespread after renal transplantation. Iron deficiency anaemia is the most common cause of anaemia, followed by acute cellular rejection.

Keywords: *Kidney transplant, Anemia, PTA, Haemoglobin, Immunosuppressive treatment.*

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INTRODUCTION

Post-renal transplant anaemia (PTA) is a common hematologic complication that can occur after renal transplantation for various reasons. The definitions of anaemia used are inconsistent. Most of the references, including WHO and the American Society of Transplantation (AST), define anaemia as haemoglobin less than 13 mg/dl for men and less than 12 mg/dl for women [1].

Nearly 30-40% of renal transplant recipients develop anaemia [2]. Nearly all patients have anaemia secondary to decreased endogenous erythropoietin (EPO) production and iron deficiency at renal transplantation. Directly after transplantation, surgical blood loss, induction immunosuppression, frequent phlebotomy, and allograft dysfunction causing a persistent uremic state contribute to continued anaemia [3]. In patients with functioning allografts, anaemia generally resolves by 3 to 6 months after transplantation. Although some patients have continuous anaemia, and late PTA, defined as anaemia developed 6 to 12 months after renal transplantation, is standard and not well studied [4].

Allograft function (eGFR) was the strongest correlate of anaemia [5]. 90% of renal transplant recipients had stages 3 - 5 CKD according to K/DOQI guidelines [6]. or confirmation of kidney damage determined by hematuria, proteinuria, interstitial fibrosis, or recurrent or de novo kidney disease.

Iron deficiency is the most common contributing factor to early PTA. Blood loss during surgery, increased iron utilization with the onset of erythropoiesis, and poor nutrition contribute to iron deficiency [7]. Other Causes of PTA include medications, renal allograft dysfunction, infections, nutritional deficiency, and rejection. There are many medications transplant recipients take that can cause anaemia. Immunosuppressive agents, antimicrobials, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin II receptor blockers (ARB) are more common culprits for suppressing erythropoiesis in the bone marrow [8].

Antiproliferative agents such as azathioprine (AZA) and mycophenolate (MMF), along with induction agents anti-thymocyte globulin (ATG) and alemtuzumab, are myelosuppressive agents that disrupt erythropoiesis by suppressing the bone marrow [9]. Agents used for infection prophylaxis, such as ganciclovir, valganciclovir, and trimethoprim-sulfamethoxazole, can also cause PTA via marrow suppression.

Transplant recipients are at a higher risk for specific viral infections that cause PTA. Infections such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and parvovirus B19 (PVB19) can cause aplastic anaemia in renal transplant recipients [10].

PATIENTS AND METHODS

This present study is a cross-sectional descriptive study; 200 renal transplant patients were conducted between Jan /2020-Jan/2021 in Shar-Hospital/Sulaymani city, depending on the online sample size calculator. The sampling method is the convenience sampling method. The data were collected through direct interviews and verbal questionnaires from the renal transplant patients who came to the dialysis Unit in Shar Hospital for regular follow-up. In addition, a detailed history was taken regarding age, gender, smoking history, history of dialysis, cause of the kidney failure, time since transplantation, history of anaemia and blood transfusion.

The enrolled patients were sent for complete blood count, and renal function and anaemic patients were sent for iron study, blood film, infection screening and Vit B12 and folate.

Inclusion criteria: Renal transplant patients who had received a renal transplant between 2010-2020 in Shar Hospital and they came for follow up. Age above 13 years

Exclusion criteria: -Pregnant ladies, patients with hemoglobinopathies, patients who underwent renal transplant before 2010, age under 13 years -Patients with haematological malignancy, patients on hemodialysis after renal transplant, patients who had received kidney transplant for the second time

Ethical consideration

Approval was taken from the ethics committee of the Kurdistan Board for Medical Specialties. Informed consent was taken verbally by the researcher from each patient enrolled in the study Confidentiality was taken into consideration.

Statistical Analysis:

All patients' data were analyzed using computerized statistical software (Statistical Package for Social

Science (SPSS version 22.0). Descriptive statistics were presented as (mean± standard deviation) and frequencies as percentages, Multiple contingency tables were conducted, and appropriate statistical tests were performed. Chi-square was used for categorical variables. An independent T-test was used to compare between means. p-value less than 0.05 was considered statistically significant.

RESULTS

Two hundred renal transplant patients were included randomly in the present study with a mean age of 45.32± 9.28 years. males were more than females, with male to female ratio as 1:7

Table (1) shows the association between Anemic & Non-anemic groups concerning Socio-demographic. There was a statistically significant association between both groups in related age (p=0.009), smoking (p=0.028), dialysis before renal transplantation (p=0.032), duration of dialysis (p=0.000) and History of Anemia before renal transplantation (p=0.001) because the result of p-value was less than 0.05. In addition, there was no statistically significant association between both groups concerning gender (p=0.676). Table (2): represents that the majority of the patients did transplantation between (Less than six months) and (1 – 2 years) which was 48.8% and 30%, respectively. Moreover, the second rank of the time since transplantation in anaemia was between (6 – 12 months) which was 17.5% of the total, while 16.7% was between (2 – 3 years) in No-Anemia cases. In addition, 96.3% and 89.2% of both groups have no history of Nephrectomy. Then,12% of the patients have a history of rejection (30% of the anaemic patients, while none of the non-anaemic patients has a history of rejection). 3.5% have a history of GIB, and all of them were anaemic. 88% of the donors were unrelated, and 12% were related. The majority of the donor age in anaemia and No-Anemia patients was between (25 – 35 years) which was 63.8% and 61.7%, respectively, and 27.5% and 28.3% were between (Less than 25 years) in anaemia and non-anaemic patients, respectively. Table (3): represents the treatment after transplantation between the two groups—the majority of the patients.

Immunosuppressant was ATG which was 90%, and 96.3% of the anaemic patients' induction was by ATG, while only 3.7%of anaemic patients' induction was by basiliximab. 72.5% and 23.8% have Ciclosporin (Sandimmune) and Tacrolimus (Prograf) in Anemic patients, respectively, while 79.2% was Ciclosporin (Sandimmune) and only 0.8% were taking Rapamune in No-Anemia. Then, 98.5% of patients had MMF (Cellcept or Myfortic) while only 1.5% had azathioprine, and the majority of the anaemic patients had MMF 97.5%, while only 2.5% of anaemic patients were on azathioprine. Regarding hypertension, 50.57% of the patients took amlodipine,33.72% took metoprolol, and only 2.3% took ACE inhibitors/ARB. Table (4) illustrates the association between the study & control group concerning recent investigations. In addition, there was a statistically significant association (differences) between both groups in related Hb (p=0.000), Platelet (p=0.019), Blood urea (p=0.000), S. Creatinine (p=0.000) and GFR (p=0.000) because the result of p-value was less than the common alpha 0.05. In addition, there was no statistically significant association (differences) between both groups concerning Wbc (p=0.914) because (p-value >0.05). Table (5) explains the association between the two groups concerning treatment after transplantation. There was a statistically significant association between both groups in related INDUCTION Immunosuppressant (p=0.016) because the resulting p-value was less than 0.05. In addition, there was no statistically significant association between both groups regarding the maintenance of immunosuppressants (p-value >0.05) Table (6) illustrates the association between Hb concerning GFR; There is a statistically significant association between Hb concerning GFR (p=0.000) because the p-value was less than 0.05.

Table 1 . Association between the two groups regarding Socio-demographic.

Items	Anemia : N = 80		No-Anemia : N = 120		Total :N = 200		Significant Test
	N	%	N	%	N	%	
Age(year)							χ2 =16.986 p=0.009
< 20	11	13.8	4	3.3	15	7.5	
20 -29	22	27.5	17	14.2	39	19.5	
30 – 39	16	20.0	34	28.3	50	25	
40 – 49	18	22.5	36	30.0	54	27	
50- 59	8	10	21	17.5	29	14.5	
±60 – 69≤	5	6.3	6	5.0	11	5.5	
≥ 70	0	0.0	2	1.7	2	1	
Mean ±SD	28.67 ± 5.76		47.78 ± 8.234		45.32 ±9.287		
Gender							χ2 =0.175 p=0.676
Male	49	61.3	77	64.2	126	63	
Female	31	38.8	43	35.8	74	37	
Smoking history							χ2 =4.805 p=0.028
Yes	2	2.5	13	10.8	15	7.5	
No	78	97.5	107	89.2	185	92.5	
Dialysis before renal transplantation							χ2 =4.604 p=0.032
Yes	65	81.3	81	67.5	146	73	
No	15	18.8	39	32.5	54	27	
If yes, the duration							χ2 =17.116 p=0.000
< 6 months	22	33.8	54	66.7	76	52.05	
6-12 months	33	50.8	24	29.6	57	39.04	
> 12 months	10	15.4	3	3.7	13	8.91	
%	**40%**		**60%**		**200**		

Table 2 . Some variables between the two groups.

Items	Anemia: N = 80		No-Anemia: N = 120		Total: N = 200	
	Frequency	%	Frequency	%	Frequency	%
Time since transplantation						
Less than six months	39	48.8	5	4.2	44	22
6 – 12 months	14	17.5	14	11.7	28	14
1 – 2 years	7	8.8	36	30.0	43	21.5
2 – 3	3	3.8	20	16.7	23	11.5
3 – 4	3	3.8	12	10.0	15	7.5
4 – 5	4	5.0	7	5.8	11	5.5
5 – 6	2	2.5	7	5.8	9	4.5
6 – 7	3	3.8	6	5.0	9	4.5
7 – 8	0	0.0	5	4.2	5	2.5
> 8	5	6.3	8	6.7	13	6.5
History of Nephrectomy						
Yes	3	3.8	13	10.8	16	8
No	77	96.3	107	89.2	184	92
Rejection history						
Yes	24	30	0	0.0	24	12
No	56	70	120	100	176	88
History of GIB						
Yes	7	8.8	0	0.0	7	3.5
No	73	91.3	120	100	193	96.5
Donor						
Related	4	5.0	20	16.7	24	12
Unrelated	76	95.0	100	83.3	176	88
Age donor(year)						
< 25	22	27.5	34	28.3	56	28
25 – 35	51	63.8	74	61.7	125	62.5
> 35	7	8.8	12	10.0	19	9.5
Total	**80**	**100**	**120**	**100**	**200**	**100**

Table 3. Treatment after transplantation between (Anemia and No-Anemia).

		Anemia : N = 80		No-Anemia:N = 120		Total :N = 200	
Items		**N**	**%**	**N**	**%**	**N**	**%**
INDUCTION Immunosuppressant							
ATG		77	96.3	103	85.8	180	90
%		42.7		57.3		180	100
BASILIXIMAB		3	3.7	17	14.2	20	10
%		15		85		20	10
Total		**80**	**100**	**120**	**100**	**200**	**100**
MAITENANCE Immunosuppressant							
A	Ciclosporin (sandimmune)	58	72.5	95	79.2	153	76.5
	Tacroliums (Prograf)	19	23.8	24	20	43	21.5
	Rapamune	3	3.7	1	0.8	4	2
B	MMF (Cellcept or Myfortic)	78	97.5	119	99.1	197	98.5
	Azathioprine (Immuran)	2	2.5	1	0.9	3	1.5
C	Prednisolone	78	97.5	119	99.1	197	98.5
	None	2	2.5	1	0.9	3	1.5
Hypertension treatment							
Amlodipine		68	50.75	64	50.39	132	50.57
Beta-blocker		49	36.57	39	30.71	88	33.72
Doxazocin		13	9.70	12	9.45	25	9.58
ACE inhibitors/ARB		3	2.24	3	2.36	6	2.30
Diltzazem		1	0.75	9	7.09	10	3.83
Total		**134**	**100**	**127**	**100**	**200**	**100**
Other treatment							
Iron Supplement/ Folic Acid		30	15.79	7	8.86	37	13.75
Valganciclovir		30	15.79	0	0	30	11.15
Anti-platelet		16	8.42	11	13.92	27	10.04
Atorvastatin		14	7.37	12	15.19	26	9.67
Esomeprazole		30	15.79	15	18.99	45	16.73
B12 injection		1	0.53	0	0	1	0.37
INH		17	8.95	0	0	17	6.32
Calcium		23	12.11	13	16.46	36	13.38
EPO/erythropoietin		8	4.21	0	0	8	2.97
Bacterium		21	11.05	21	26.58	42	15.61
Total		**190**	**100**	**79**	**100**	**269**	**100**

Table 4. The association between the two groups concerning recent investigations.

Items	Anemia : N = 80		No-Anemia : N = 120		Total : N= 200		Significant Test
	N	%	N	%	N	%	
Hb(g/dL)							
< 13	80	100	0	0.0	80	40	
13– 16	0	0.0	112	93.3	112	56	χ2=200.001 p=0.000
> 16	0	0.0	8	6.7	8	4	
Mean ±SD	9.87 ± 1.62		13.89 ± 1.32				
WBC							
< 4,000	25	31.3	37	30.8	62	31	
4,000 – 12,000	53	66.3	81	67.5	134	67	χ2=0.181 p=0.914
≥ 12,000	2	2.5	2	1.7	4	2	
Mean ±SD	5550.00 ± 2306.9		4957.38±3239.82				
Platelet							
< 150,000	30	37.5	24	20.0	54	27	
150,000 – 400,000	50	62.5	95	79.2	145	72.5	χ2=7.95 p=0.019
≥400,000	0	0.0	1	0.8	1	0.5	
Mean ±SD	167643.75 ± 0699.1		214916.67 ± 89877.94				
Blood urea(mg/dL)							
<40	25	31.2	107	89.2	132	66.0	χ2=71.751 p=0.0000
> 40	55	68.8	13	10.8	68	34.0	
Mean ± SD	60.03 ± 41.8		31.13 ± 7.7				
S. Creatinine (mg/dL)							
< 1.1	28	35.0	119	99.2	147	73.5	
1.2 – 2.0	30	37.5	1	0.8	31	15.5	
2.1 – 3.0	11	13.8	0	0.0	11	5.5	χ2=101.523 p=0.0000
3.1 – 4	2	2.5	0	0.0	2	1	
> 4.0	9	11.3	0	0.0	9	4.5	
Mean ± SD	2.03±1.53		0.84 ± 0.17				
Total	**80**	**100**	**114**	**100**	**200**	**100**	

Table 5. Association between the two groups and treatment after transplantation.

Items		Case: Anemia N=80	%	No-Anemia N=120	%	Total	Significant test
INDUCTION Immunosuppressant							
ATG		77	96.3	103	85.8	180	χ2 =5.787 p= 0.016
BASILIXIMAB		3	3.7	17	14.2	20	
MAITENANCE Immunosuppressant							
A	Ciclosporin (sandimmune)	58	72.5	95	79.2	153	χ2 =2.634 p= 0.268
	Tacroliums (Prograf)	19	23.8	24	20	43	
	Rapamune	3	3.7	1	0.8	4	
B	MMF (Cellcept or Myfortic)	78	97.5	119	99.1	3	χ2 =0.902 p= 0.342
	Azathioprine (Immuran)	2	2.5	1	0.9	197	
C	Prednisolone	78	97.5	119	99.1	3	χ2 =0.902 p= 0.342
	None	2	2.5	1	0.9	197	

Table 6. Association between Hb in and GFR.

CKD-Stage	GFRCKD-EPI (ml/ min/1.73m2)	Hb(g/dL) < 13 N	%	13 – 16 N	%	> 16 N	%	Total	Significant Test
G1	>= 90	13	16.25	90	80.36	8	100	111	
G2	60 – 89	14	17.5	18	16.07	0	0.0	32	
G3a	45-59	16	20	4	3.57	0	0.0	20	
G3b	30-44	17	21.25	0	0.0	0	0.0	17	χ2 =107.851 p= 0.000
G4	15-29	11	13.75	0	0.0	0	0.0	11	
G5	<15	9	11.25	0	0.0	0	0.0	9	
Total		**80**	**100**	**112**	**100**	**8**	**100**	**200**	

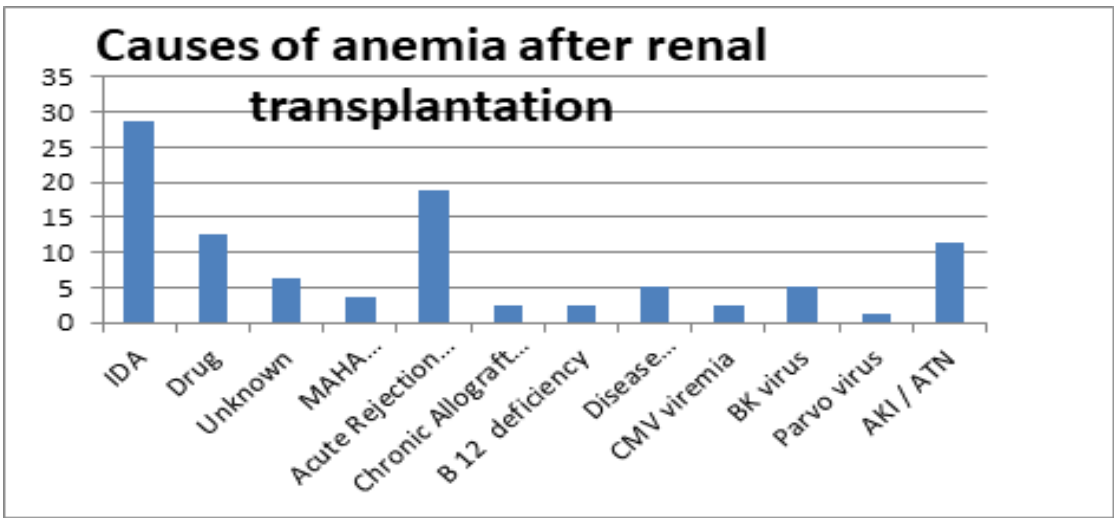

Figure 1. Causes of anaemia after renal transplantation.

DISCUSSION

Anaemia after kidney transplant is a topic of increasing interest; in this cross-sectional descriptive study, 200 patients were included, 126(63%) patients were males, and 74(37%) patients were females, with a male to female ratio of 1.7. Age ranged from 14-70 years with a mean of 45.32±9.28; our study demonstrated that PTA is remarkably high at 40% (table 1). This result is close to a study done in turkey in which the prevalence of PTA was 37.5% [11].

Our study did not show a significant difference by gender regarding PTA (table 1) in contrast to a study done in Saudi Arabi in which PTA is higher in female patients [12].

The current study shows that anaemia is more common in young patients at 27.5% (Table 1); this can be because most participants were young, between 20-29 years and 30-39 years, 19.5% and 25%, respectively. In our study history of smoking is higher in the non-anaemic group 10.8%, and it has a statistically significant association with PTA (p=0.028) (Table 1)

There has been a highly significant association between anaemia and time since renal transplantation in the present study. Anaemia is much higher in the first six months post-transplant, 91% (p=0.000) (Table 2). This result is consistent with a European survey done by Ponticelli et al. [13] ,and can be explained by surgical blood loss, and acute rejection episodes occur mainly during this period, and the patients take high dose immunosuppression during this period.

After renal transplantation, many risk factors contribute to PTA. GFR decline for any reason (rejection, ATN, viral infection) is significantly associated with anaemia (14); the lower the GFR, the higher NO of anaemic patients (p=0.000) (table 6). Another risk factor is the history of rejection (ACR or AMR). In the present study, PTA is significantly higher in those patients who have a history of rejection (p= 000) (Table 5); this result is consistent with a study done by Schechter A and Graftre Gvili A [15].

Types of immunosuppression medications such as induction or maintenance treatment are a significant cause of PTA because some of them affect the bone marrow, causing bone marrow suppression [16]. In our study majority of the patients were inducted by ATG, which was 90%, and basiliximab, which was 10%, and PTA is more common among those whom ATG was inducted. The association was very significant(p=0.016) (Table 3).

Azathioprine and MMF are immunosuppressive drugs that may induce anaemia; in this study, most of the patients were taking MMF at 98.5% and azathioprine at 1.5%; there is no significant difference in the development of anaemia in both groups; this may be due to that only a few patients were on azathioprine 3(1.5%) (Table 4).

Our study did not find a correlation between the use of ACEI and ARB with PTA (Table 4); very few patients can explain this were on ACEI and ARB, contrary to a study done by Gossman J showed that the use of ACEI and ARB was associated with anaemia [17].

Regarding causes of anaemia, our study showed that Iron deficiency anaemia (IDA) is the most common cause of PTA. It accounts for 28.75%, which is consistent with other studies done by Schechter A [18], then acute rejection (ACR+AMR) is the second most common cause of PTA; it is explained by GFR decline and the effect of intense immunosuppression drugs using in rejection episodes (Table 6). Then effects of immunosuppressive drugs and AKI/ATN account for 12.5% and 11.25%, nutritional deficiencies (Vit B12), and viral infections, including BKV and CMV, account for .5%and 7.5%, respectively Figure (1). Microangiopathic hemolytic anaemia (MAHA) and chronic allograft nephropathy (CAN) account for only 3.75% and 2.5% of the causes in our study.

Our findings should encourage nephrologists to evaluate patients with anaemia thoroughly; even for mild anaemia, infections and rejection should be excluded, and metabolic deficiencies should be assessed.

Limitations of the study include a single-centre study. No, follow up for management. the short duration of study time

CONCLUSION

The present study showed that anaemia is a common complication after renal transplantation, especially in the first six months; this is mainly due to perioperative blood loss, iron deficiency anaemia, rejection episodes (ACR and AMR), and graft dysfunction, effects of high dose immunosuppression medications in this period. Furthermore, our study showed a very significant association between eGFR and PTA.

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