MERIT RESEARCH JOURNALS
www.meritresearchjournals.org
Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 6(7) pp. 265-271, July, 2018
Available online http://www.meritresearchjournals.org/mms/index.htm

Original Research Article

The Incidence of Neutropenia Post Kidney Transplant Patient at Prince Sultan Military Medical City

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Abstract

There are indirect evidences showed that there is an association between neutropenia and some of the medications such as Anti-thymocyte Globulin (ATG), Mycophenolic acid (MPA) and Tacrolimus (TAC) that are use for kidney transplant patients. It is evidenced that are driven upon reducing dose or holding these medications. The prolonged and severe neutropenia can lead to serious infections and allograft rejection. A retrospective cohort study where patients had been tackled over six months post kidney transplantation. The 81 patients who had transplantation between January 2014 and December 2014 were identified and followed up using hospital system and patients medical records. The incidence of neutropenia was 11.11%. The findings show an association between neutropenia post kidney transplant and some factors including: female gender and the use of immunosuppressant medications, like MPA (P<0.05). Eighty one patients were tackled retrospectively for 6 months. The incidence of neutropenia were 11.11%. TAC and MPA were used in all of patients. This study claimed that these medications might increase the risk of neutropenia post kidney transplant; P<0.05. The findings of the present study indicate the holding MPA and using G-CSF is significantly effective to accelerate the recovery of neutropenia. The incidence of neutropenia in this study was relatively high post kidney transplant with female gender and MPA alone or in combination with TAC being potentially associated factors with neutropenia.

Keywords: Neutropenia, Kidney transplant, Medication, Immunosuppressant

INTRODUCTION

Neutropenia is a disease that is relatively common in post kidney transplant patients. It is defined by the deficiency in neutrophils count, especially when neutrophils count become 1500 or less cells/µL (Coates T, 2015; Yang et al., 2015). Neutropenia is classified as mild, moderate, or severe, based on the absolute neutrophils count (ANC). Where the mild is between 1000-1500 cells/µL, moderate 500-1000/µL, and the severe is less than 500 cells/µL (Coates T, 2015; Yang et al., 2015).

Neutropenia results from the following: inefficient is an association between neutropenia and medications that used in kidney transplant including; the potent neutrophil production, granulopoiesis deficiency, move of circulating neutrophils to the vascular endothelium or tissue pools and/or increasing the peripheral destruction (Zafrani et al., 2009). Bone marrow toxicity causes neutropenia. That is arising from some medications, systemic infection or post-transplant lymph proliferative disease (Zafrani et al., 2009). The prevalence of neutropenia worldwide in kidney transplant patient ranges between 4.9% to 37.5% (Zafrani et al., 2009; Hurst et al., 2011; Savvidaki et al., 2014). Evidence shows that there lymphocyte proliferation inhibitor like Mycophenolic acid (MPA) and Valganocyclovir, and medications with

neutropenic effect such as anti-thymocyte Globulin (ATG), Tacrolimus (TAC), Sirolimus, Cotrimoxazole, Rituximab, omeprazole and Angiotensin converting enzyme inhibitors (Zafrani et al., 2009; Hurst et al., 2011; Savvidaki et al., 2014; Hurst et al., 2011; Savvidaki et al., 2014; Hong JC and Kahan BD, 2000; Keisu et al., 1990; Gabutti et al., 1999; Schulz et al., 2005).

Despite the importance of these medications and its roles in kidney transplantation, it has been suggested that these induction and prophylaxis treatments have its role on neutropenia incidence. However, there is no clear evidence shows an association between neutropenia in post kidney transplant patients and these medications. It is only indirect evidence that is driven upon reducing or holding them in practice (Yang et al., 2015; Rerolle et al., 2007; Matsui et al., 2010).

The prolonged and severe neutropenia can lead to serious infection and allograft rejection (Zafrani et al., 2009; Savvidaki et al., 2014). This study aims to measure the neutropenia incidence and its associated factors, in order to assess the severity of neutropenia and the outcomes in patients had kidney trans-plantation at Prince Sultan Military Medical City (PSMMC.)

METHODS

Subjects and Setting

Study design

A retrospective cohort study design using patients' medical record number (MRN) to tackle patients on hospital database system for patients who had kidney transplant at PSMMC(renal transplant unit)from January2014 to December 2014.
This hospital is servicing large population in Saudi Arabia.

Inclusion criteria

- All adult patients who had kidney transplant at PSMMC between January 2014 to December 2014.

Exclusion criteria

- Patients who had kidney transplantation outside PSMMC.
- Patients with inadequate initial or follow up data**.**

Ethical Approval

The proposal was submitted to the research center at Prince Sultan Military Medical City (PSMMC) for ethical approval.

Data collection and handling

Neutropenia was defined when patients have neutrophils count ≤ 1500cells/µL for three days or when the mean is less or equal than 1500cells/µL, mild when neutrophils count 1500 – 1000cells/µL, moderate neutrophils count = 1000 – 500cells/µL, sever when neutrophils count ≤ 500cells/µL (Coates T, 2015).

FK level was defined optimal when patients has FK range between 8 to 12µg/L post the transplantation , more than 15 µg /L toxic level regarding to the hospital protocol.

Concomitant medications all patients were received prophylaxis therapy in the first 3 months which are : (valganciclovir for cytomegalovirus, trimethoprim and sulfamethoxazole for bacterial infection and ciprofloxacin for Urinary tract infection).

The significance level used in this study is 0.05 and results will be considered significant if ($P<0.05$).

Data collection

The identified patients were followed up in a daily bases during admission, weekly during the first months, every two weeks from the 4^{th} month over the six months post the transplantation day, using MRN and a designated-form that includes individual patients' demographics and clinical features:, gender, white blood count, neutrophils count, FK level… etc.,

For patient's confidentiality and anonymity of research respondents the patients were assigned to a serial number separate from their MRN.

Data analysis

Population description

Descriptive analyses, like median and percentages, were calculated for the aggregated data to describe the identified sample. Additionally, the association of some factors were assessed, these factors includes: gender, recipient and donor age, previous kidney transplants, blood type, living related donor, and their immunosuppressive medications. Descriptive statistical tests such as Chi-square tests and Fisher Exact test were used when needed.

RESULTS

Eighty one patients were identified who had renal

Table 1. Patients' characteristics (n=81 patients)

Characteristic; N=81	**n**	**%**
Gender		
Female	31	38.3%
Male	50	61.7%
Age (on admission)	**Average ± SD**	**(range)**
All	44 ± 14	(15-74)
Female	44 ± 12	(18-74)
Male	45± 15	(15-72)
Blood type	**n**	
A	24	29.6%
B	11	13.6%
AB	4	4.9%
O	42	51.9%
Kidney transplant status		
1st time	78	96.3%
2nd time	3	3.7%

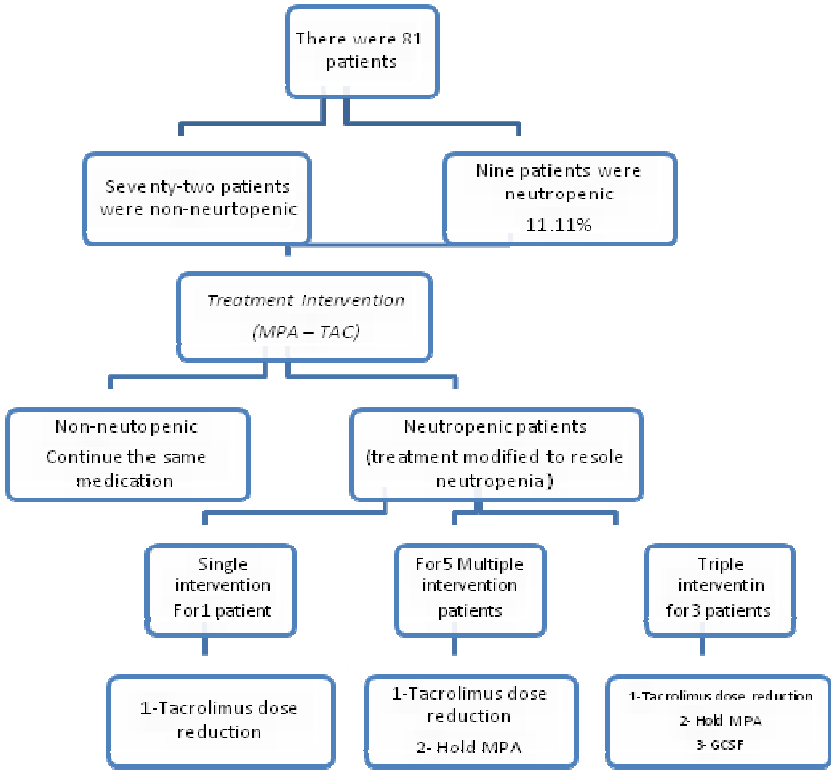

Figure 1. Demographic features in the transplanted patients

transplantation, Male was the dominant gender of the studied sample (61.7%), with average age of 45 years. The demographic features of the defined patients are shown in Figure-1 and Table-1.

Comparison between neutropenic and non-neutropenic patients

Out of 81 renal transplant patient, 9 (11.1%) had neutropenia incidence at least once, the patients who had two or more episode were measured as one time in the analysis, the clinical and demographic differences between neutropenic and non-neutropenic patients were mentioned simply (Table-2).

Female gender

The incidence rate of neutropenia was higher with female (12.9%), while male were at lower incidence rate (10.0%), as shown in figure-3.

Table 2. The Demographic and Clinical Deferences between Neutropenic and Non-neutropenic Patients

Characteristics N=81	Neutropenic (n=9)	Non-neutropenic (n=72)	P-value
Kidney transplant status	**n(%)**	**n (%)**	0.454
1st time	8 (9.9%)	70 (86.4%)	
2nd time	1 (33.3%)	2 (66.7%)	
Gender			0.475
Female	4 (12.9%)	27 (87.1%)	
Male	5 (10.0%)	45 (90.0%)	
Recipients age grouping (years)			
15-34	5 (23.8%)	16 (76.2%)	
35-54	2 (4.9%)	39 (95.1%)	
55-74	2 (10.5%)	17(89.5%)	
Donors age grouping (years)			
18-29	6 (13.3%)	39 (86.7%)	
30-39	1 (4.3%)	22 (95.7%)	
≥ 40	3 (20.0%)	12 (80.0%)	
Living-related donor			0.354
In relation	6 (10.7%)	50 (89.3%)	
No relation	0	9 (100.0%)	
Cadaveric	3 (18.7%)	13 (81.3%)	
Immunosuppressant and induction therapy			
MPA	9 (11.1%)	72 (88.9%)	<0.005
Tacrolimus	9 (11.1%)	72 (88.9%)	<0.005
ATG	9 (12.2%)	65 (87.8%)	0.424

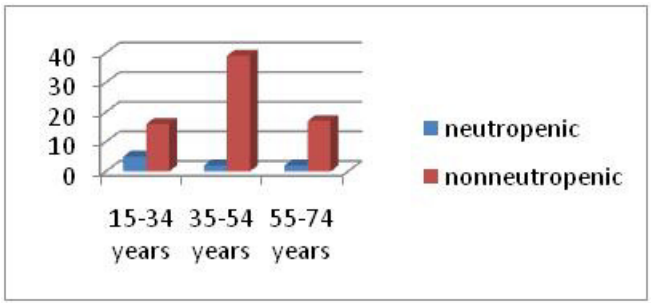

Figure 2. Age of Neutropenic and Non-neutropenic Patients

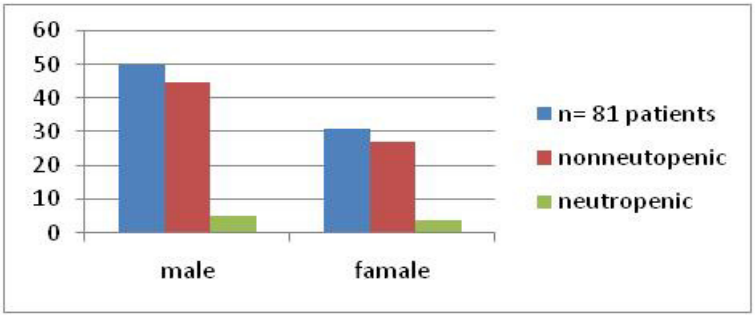

Figure 3. Neutropenia Incidence Rate with Gender

FK -506 level

Tacrolimas was measured by the FK level, to avoid any toxicity Out of nine neutropenic patients, eight were in the optimal range and they had neutropenia at least once. However, the FK level does not show any significant effect P = 0.162.

Table 3. The incidence of neutropenia inrelation with FK-506level

FK-506 level	Neutropenic n%	Non-neutropenic n%
Optimal level	8 (12.3%)	57 (87.7%)
High level	1 (6.3%)	15 (93.7%)

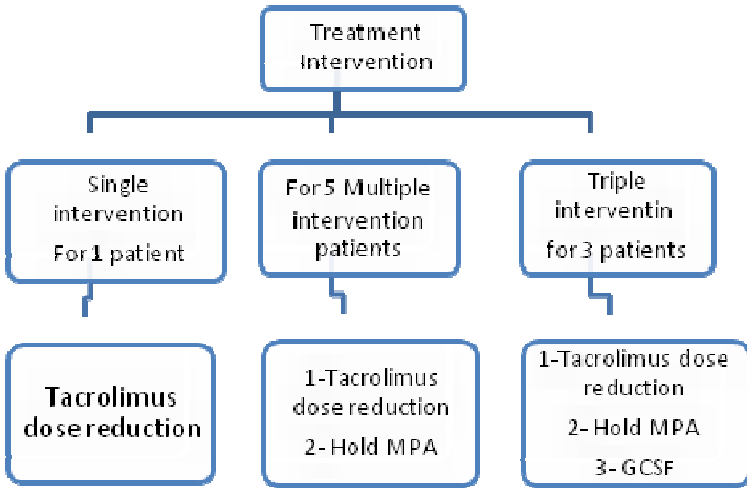

Figure 4. Treatment intervention that has been used throughout thye study

MPA

All of the patients received MPA, 59 were using MMF, 7 had neutropenia (11.9%) and 22 were using EC-MMF, two had neutropenia (9.1%); however, there was no deference between them in term of neutropenia risk. However, patients who received higher doses of MPA were more susceptible to neutropenia.

Induction therapy

ATG was given before kidney transplantation, which may increase the risk of having neutropenia. All of the neutropenic patients received ATG as induction therapy. Only 7 out of 81 patients have not received ATG and they haven't had neutropeniaepisode, P= 0.424.

Severity of Neutropenia

Four patients had mild neutropenia, another four had moderate neutropenia and only one patient had severe neutropenia. All of these patients had neutropenia episode in the first six months post kidney transplant.

Infection

All the patients were receiving concomitant medications as prophylaxis at the first three months. Fortunately, the majority of patients have no infections at the followed up period.

Treatment Intervention

Patients who received GCSF have improved in ≤ 7 days and no allograft rejection was recorded (Figure 4).

Hospital readmission post kidney transplant

The majority of patients who readmitted to the hospital were having neutropenia.

DISCUSSION

Several studies show conflict of neutropenia incidence in post kidney transplant. This study aimed to measure neutropenia incidence, especially there is no studies conducted in Saudi Arabia.

Eighty one patients in PSMMC were followed up retrospectively for six months. The incidence of neutropenia was 11.11%. Eirini et al reported that the incidence of neutropenia for kidney transplant patients in the conducted studies were between 10% to 55.5%, while L.Zafrani et al reported that the incidence is in range between 4.9% and 37.5%. L.Zafrani et al study itself shows an incidence of 28% in those patients who had kidney transplant. Frank et al have measured an

incidence of 14.5% from patients had kidney transplant. The findings were consistent with other studies. The incidence of neutropenia was associated with some factors such as gender; female gender was at higher risk of having neutropenia than male. Although this study has not recorded any significant impact of gender in the incidence of neutropenia, like L.Zafrani et al who pointed out that female might be a risk factor although their result was not statistically significant P= 0.71. However, Frank et al has showed that female gender was an associated factor with neutropenia and it was statistically significant P< 0.001. These differences in p-value might be due to the sample size; the sample in this study was only 81 patients Vs41705 patients in Frank et al study. Additionally, the gender ratio of the studied sample might be another explanation. There were only 31 female in the 81 patients.

TAC and MPA were used in all of patients. This study claimed that these two medications might increase the risk of neutropenia in post kidney transplant; P<0.05, The finding was consistent with L.Zafrani et al, Frank et al (p-value < 0.001) and Eirini et al (P < 0.001). They gave an explanation by the possibility of drug-interaction between TAC and MPA which might increase the bioavail-ability of MPA which lead to increase the risk of neutropenia.

ATG which is induction therapy used pre-transplantation as a prophylaxis for acute kidney rejection. In this study the ATG has not showed any direct effect in neutropenia P=0.424 however, there was eight patients have not received ATG due to the completely matching with the donors. In those patients no neutropenia have been recorded. L.Zafrani et al study revealed that there is a significant association between ATG and neutropenia (P=0.049). Frank et al highlighted that ATG might induce neutropenia at higher rate than IL-2 antagonist. Also, D.Brennan et al study showed that ATG might induce neutropenia more frequently than Basiliximab.

The findings of the present study indicate the holding of MPA. And using G-CSF is significantly effective to accelerate the recovery of neutropenia which is consistent with L.Zafrani et al study and many others.

One of the limitations in this study was the sample size due to the limited period for data collection. Also, ANC was not measured regarding to the hospital database which is not including the differential neutrophils count.

This study shows that there might be a relation between blood O type and neutropenia, which is a point that is recommended to evaluate in other studies.

CONCLUSION

The incidence of neutropenia in our study was relatively high in post kidney transplant in female gender under MPA alone or in combination with TAC being potentially associated factors with neutropenia. Additionally, using G-CSF in persistent neutropenia could be safe with close monitoring.

ACKNOWLEDGMENTS

We would like to thank Dr. Hadah Alkhaldi for her guidance, support and advice that were given during this project. We would like to thank Dr. Mohammed Alwaily and The Renal Transplant Unit (Amro Al Abotayer and mohammed bin Salem), for helping us to collect the patients data. The financial support of Prince Nourah bint Abdulrahman University is gratefully acknowledged.

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