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Original Article

The association between tacrolimus blood levels and possible neurotoxicity following liver transplantation

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Abstract

Aim: Tacrolimus is an immunosuppressive agent used for prophylaxis of organ rejection after solid organ transplantations. Neuropsychiatric adverse effects that occur in the first 4 weeks following initiation of tacrolimus defined as early tacrolimus-induced neurotoxicity (TIN). In our study, we aimed to determine the incidence of possible TIN and to examine its association with tacrolimus blood levels and establish other medical and clinical factors to predict in patients with liver transplantation.

Material and Methods: This retrospective, single-center study was conducted at a transplantation unit of tertiary level university hospital. All the patients were enrolled, who undergone liver transplantation between January 2013 and December 2018. Tacrolimus blood levels were obtained the day after the initiation of tacrolimus and for consecutive 10 days. All the patients z-scores calculated for tacrolimus mean blood levels until index day. Index day is defined as 'the day of diagnosis of possible TIN'. Age, gender, previous encephalopathy, cadaveric/live donor transplantation, pre-transplantation MELD score, CRP levels and tacrolimus blood levels were investigated as predictors of possible neuropsychiatric events following liver transplantation in two weeks.

Results: Tacrolimus z-scores were detected to be significantly different between groups; found to be lower in the possible tacrolimus-induced neurotoxicity group compared to the control group (t=2.607, p=0.01). Pre-transplantation model significantly predicts neuropsychiatric adverse events($\chi^2(7)=16.049$, p=0.035).

Conclusion: To our knowledge, this is the first study that shows an inverse association with tacrolimus blood levels and possible TIN; which requires consideration. It is obvious that further well designed, prospective studies are needed to clearly establish risk factors for TIN.

Keywords: Tacrolimus; neurotoxicity; liver transplantation.

INTRODUCTION

Tacrolimus is a calcineurin inhibitor which is an effective immunosuppressive agent that is used routinely after solid organ transplantations. Tacrolimus improve the survival rates and outcomes of solid organ transplantations however with some critical adverse effects; namely nephrotoxicity and neurotoxicity (1). Adverse neurological and psychiatric events after liver transplantation may occur in the first month with an estimated incidence of 40% after transplantation and especially common in liver transplantation recipients (2). Adverse neuropsychiatric events that occur in 4 weeks and in the context of tacrolimus can be defined as early tacrolimus-induced neurotoxicity (TIN) (3). Adverse neuropsychiatric events due to TIN can be problematic and have important outcomes such as increased morbidity and even mortality (4).

Although, in literature TIN seems to be a well-defined clinical entity, practically there is no clear diagnostic tool or any cue for clinicians apart from retrospective diagnosis by dose reduction or withdrawn of the agent. The diagnosis of TIN is associated with critical decisions such as withdrawal or dose reduction of the agent;

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which could increase the risk of allograft rejection and infections. The diagnosis of TIN seems to be an exclusion diagnosis, with an exception of high tacrolimus blood levels (15 ng/ml and over). The presentation of symptoms differs widely among patients and the diagnosis of this condition is a challenge for clinicians and this issue is not properly addressed in the current literature (5). Therefore, we suggest using 'possible tacrolimus-induced neurotoxicity' for patients without any proven diagnosis.

Etiopathogenesis of TIN is still not clear (4,6). Intracerebral tacrolimus levels, white blood tacrolimus levels and tacrolimus blood levels were reported to be correlated with TIN severity however with conflicting results (7,8). Indeed, transplantation patients can show TIN symptoms even if the tacrolimus blood levels in the therapeutic range (4,9). Many risk factors are also suggested for TIN; such as previous hepatic encephalopathy, history of neuropsychiatric disorders, pre-transplantation MELD scores, age and some metabolic parameters (10,11). Unfortunately, literature is scarce and there is a need to establish risk factors clearly and improve our understanding of this relatively common neuropsychiatric disorder.

In our study, we aimed to determine the incidence of possible TIN and to examine its association with tacrolimus blood levels and establish other medical and clinical factors to predict in patients with liver transplantation. We hypothesized that; higher tacrolimus levels (although levels are in therapeutic range) could be associated with higher neurotoxicity risk in patients with liver transplantation.

MATERIAL and METHODS

This retrospective, single-center study was conducted at a transplantation unit of tertiary level university hospital. All the patients were enrolled, who undergone to liver transplantation between January 2013 and December 2018.

Patients' sociodemographic and clinical characteristics were obtained through our database. The items included to our study were; age, gender, BMI, pre-transplantation MELD score, Hb levels, pre and post-transplantation sodium, platelet count, albumin, protrombin, INR, bilirubin ALT, AST, CRP levels, creatinine levels, type of transplantation (cadaveric/live donor), previous encephalopathy, hypertension and diabetes mellitus.

Assessment of Tacrolimus Blood Levels

Tacrolimus blood levels were obtained the day after the initiation of tacrolimus and for consecutive 10 days. Mean values of tacrolimus blood levels were obtained for each subject until the index day. Index day is defined as 'the day of diagnosis of possible TIN'. For control group, mean value of tacrolimus blood levels for 10 days were calculated. After that, for each participant; z-score assigned. For TIN group, z-score is calculated for index day as mean summation from the first day to the index day. If an index day were diagnosed before 10 days, than only blood values to that day were take into account and other blood values were withdrawn from further analysis.

Diagnosis of Possible TIN

We reviewed all the patients' records and first, we identified the patients who consulted to the psychiatry or neurology in 14 days following liver transplantation. After that, experienced clinicians reviewed the consultation records and some of the patients were diagnosed with 'possible TIN'. The day the patient consulted to the neurology or psychiatry were identified as index day, as previously mentioned. As a result, we classified all the patients into two groups: 'possible TIN' and 'control'. Flowchart is given in Figure-1.

Statistical analyses

Descriptive variables were given as mean±SD, median (min-max) and n (%) depending on the variable. Groups were compared by using Mann-Whitney U test for nonparametric analysis, Student-t test for continuous variables and chi-square test for categorical variables. Shapiro-Wilk test for normality were used to assess distribution of normality.

Binary logistic regression analysis was used to predict possible tacrolimus-induced neurotoxicity. Age, gender, previous encephalopathy, cadaveric/ live donor transplantation, pre-tx MELD score, pre-tx CRP levels, post-tx creatinine levels were included into the model. Associations were given as odds ratio (OR) with 95% confidence intervals (CI).

Spearman correlation analyses were done for tacrolimus z-scores with pre-tx and post-tx variables (CRP, WBC count, ALT, AST, creatinine, sodium and potassium levels). For categorical variables such as previous hypertension, diabetes mellitus, encephalopathy, cadaveric/live donor transplantation groups were created and each group were compared for tacrolimus blood level z-scores by using Mann-Whitney U test.

Statistical significance threshold was established as $p<0.05$. SPSS pocket program (SPSS, version 23.0 for Windows; Chicago, IL) was used. Our retrospective analysis was conducted in line with Helsinki declaration ethical standards and with required permissions.

RESULTS

A total of 144 patients were included into our study. Demographic and medical variables of the sample are given in Table-1. No statistically significant difference was detected between groups when compared by age, gender, BMI, MELD score, pre-transplantation Hb, creatinine, sodium, platelet count, albumin, prothrombin time, INR, bilirubin, ALT, AST, CRP levels, cadaveric/ live organ donation, previous encephalopathy, hypertension, diabetes mellitus rates, duration of intensive care. Merely 6.3% (n=9) of our sample were diagnosed with ethanol-related cirrhosis which limits our further analysis between groups according to the primary diagnosis. Only tacrolimus z-scores were detected to be significantly different between groups; tends to be lower in possible tacrolimus-induced neurotoxicity group compared to control group ($t=2.607$, $p=0.01$).

According to the correlation analyses, only pre-

transplantation Hb and post-transplantation CRP levels were significantly correlated with tacrolimus blood levels z-scores; no significant correlations were found between tacrolimus blood levels z-scores and other pre-transplantation and post-transplantation variables (Table-2 and Table-3).

Binary logistic regression analysis was performed to predict possible tacrolimus-induced neurotoxicity using pre-transplantation variables age, gender, previous encephalopathy, cadaveric/live donor transplantation, pre-transplantation MELD score, pre-transplantation CRP levels and blood tacrolimus levels z-scores (n=111). Model was statistically significant ($\chi^2(7)=16.049$, p=0.035), explained 19.9% (Nagelkerke R^2) of the variance and correctly classified 76.6% of cases. Results were given in Table-4. Also, binary logistic regression analysis was performed to predict possible TIN using post-tx variables; post-tx sodium and post-tx potassium levels and blood tacrolimus levels z-scores (n=61). Model was statistically significant ($\chi^2(3)=17.510$,p=0.001), explained 34.9% (Nagelkerke R^2) of the variance and correctly classified 76.7% of cases. Only post-tx potassium levels significantly added to the model. Results were given in Table-5.

Tacrolimus blood levels z-scores were compared between groups for previous hypertension, diabetes mellitus, encephalopathy and cadaveric/live donor transplantation. When compared with non-hypertension group, hypertensive patient's tacrolimus blood levels z-scores were significantly lower (U=490.5, p=0.01). No statistically significant difference were found between diabetic/non diabetic, positive/negative encephalopathy history or cadaveric and live organ transplantation donors (U=1833.5, p=0.437; U=2003, p=0.275; U=1365, p=0.518 respectively). 1.

Table 1. Demographic and Medical Variables

	All (n=144)	Possible TIN (n=40)	Control (n=104)	X^2 , t, U	p value
Age	50.16±12.13 53.5(16-70)	50.48 ±14.74 55(18-70)	50.04 ±11.18 52 (16-67)	U=1908	0.443
Gender (Male/Female)	58.3%/41.7%	52.5%/47.5%	60.6%/ 39.4%	X^2=0.775	0.379
Body Mass Index	27.09±5.56	27.37±5.78	26.99±5.51	t=-0.322	0.748
MELD score	18.67±8.43 16(6-48)	20.79± 9.1 20(10-39)	17.97± 8.12 14.5(6-40)	U=1020.5	0.124
Hemoglobuline	10.73±2.21	10.7± 1.82	10.74±2.34	t=0.095	0.925
Creatinine	0.89± 0.54 0.78 (0.35-3.85)	1.05± 0.78 0.85 (0.44-3.85)	0.84± 0.42 0.77 (0.35-2.14)	U=1473.5	0.189
Sodium	136.38± 5.22 137 (120-158)	136.47± 4.13 137 (132-149)	136.35 ±5.61 138 (121-158)	U=1221.5	0.505
Platelet Count	95.46± 63.28 77(18-349)	92.46± 76.9 69 (20-349)	96.52±58.12 74 (18-239)	U=1497.5	0.234
Albumine	2.99± 0.53	2.92± 0.46	3.02± 0.55	t=0.944	0.347
Prothrombin Time	6.49± 1	6.34± 1.03	6.55± 0.99	t=1.048	0.296
INR	1.73± 0.83 1.49(0.91-6.83)	1.99± 1.26 1.5 (1.08-6.83)	1.63± 0.59 1.5(0.91- 3.59)	U=1525	0.293
Bilirubine	5.42± 7.28 2.9 (0.21-35.87)	6.19± 7.68 3.33 (0.89-30.2)	5.15± 7.15 2.38 (0.21-35.31)	U=1430.5	0.126
ALT	168.7± 688.9 30 (6-5301)	413.86± 1263.8 30 (13-5301)	82.03± 246.84 30 (6-2087)	U=1679	0.786
AST	195.47±827.3 48 (16-7854)	489.06± 1577.3 48 (26-7854)	91.68 ±154.97 48 (16-1116)	U=1592.5	0.478
CRP	13.04± 17.08 6.65(0.3-91.2)	20.1± 25.249.5 (1.3-91.2)	10.49± 12.14 5.15 (0.3-58.8)	U=1254	0.06
Cadaveric donor rate	17.4%	10%	20.2%	X^2=2.092	0.148
Previous Encephalopathy	33.8%	40%	31.4%	X^2=0.956	0.328
Hypertension	10.4%	15.4%	8.3%	X^2=1.484	0.223
Post-transplantation Sodium	137.7±5.3 138 (122-149)	138.9± 4.3 139 (129-149)	135.5±6.2 137 (122-148)	U=275	**0.027**
Post-transplantation Potassium	4.11± 0.8	3.8± 0.7	4.6± 0.8	t=4.044	**<0.001**
Diabetes Mellitus	31.6%	30.8%	32%	X^2=0.018	0.893
Intensive care duration(days)	3.5 (1-29)	4 (2-29)	3 (1-23)	U=1026	0.742
Tacrolimus z-score	-0.09± 0.97	-0.42± 0.76	0.04± 1.01	t=2.607	**0.01**

*Mean±SD; median (min-max), rate (%) are given as appropriately.
**For categorical variables X^2, for nonparametric analyses Mann-Whitney U and for continuous variables Student-t test are used appropriately.

Table 2. Correlations between post-transplantation variables and blood tacrolimus levels z-scores

	Creatinine	CRP	White Blood Cell	ALT	AST	Sodium
Tacrolimus z-score	r=0.09, p=0.946	r=0.286, p=0.029	r=0.203, p=0.116	r=0.098, p=0.454	r=0.148, p=0.256	r=0.042, p=0.748

Table 3. Correlations between pre-transplantation variables and blood tacrolimus levels z-scores

	Age	Hemoglobuline	Creatinine	Sodium	Platelet Count	Albumine
Tacrolimus z-score	r=0.09, p=0.946	r=0.197, p=0.023	r=0.203, p=0.116	r=0.098, p=0.454	r=0.148, p=0.256	
	INR	**Bilirubine**	**ALT**	**AST**	**CRP**	**ProthrombinTime**
	r=0.02, p=0.823	r=-0.01, p=0.908	r=0.021, p=0.806	r=0.045, p=0.606	r=-0.006, =0.945	r=0.021, p=0.872

Table 4. Pre-transplantation risk factors associated with possible TIN

	B	SE	OR (95% CI)	p-value
Age	0.007	0.02	1.01 (0.97-1.05)	0.729
Gender	-0.633	0.486	0.531 (0.205-1.376)	0.193
Previous Encephalopathy	0.446	0.587	1.56 (0.5-4.94)	0.447
Cadaveric/ live donor transplantation	-1.238	0.587	0.29 (0.06-1.45)	0.132
Pre-transplantation MELD score	0.029	0.035	1.03 (0.96-1.1)	0.409
Pre-transplantation CRP	0.031	0.014	1.03 (1-1.06)	0.024
Blood tacrolimus levels z-score	-0.586	0.272	0.56 (0.33-0.95)	0.031

Table 5. Post-transplantation risk factors associated with possible tacrolimus neurotoxicity

	B	SE	OR (95% CI)	p-value
Post-transplantation Sodium	0.069	0.075	1.07 (0.93-1.24)	0.354
Post-transplantation Potasium	-1.353	0.488	0.26 (0.1-0.67)	0.006
Blood tacrolimus levels z-score	-0.582	0.394	0.56 (0.26-1.21)	0.140

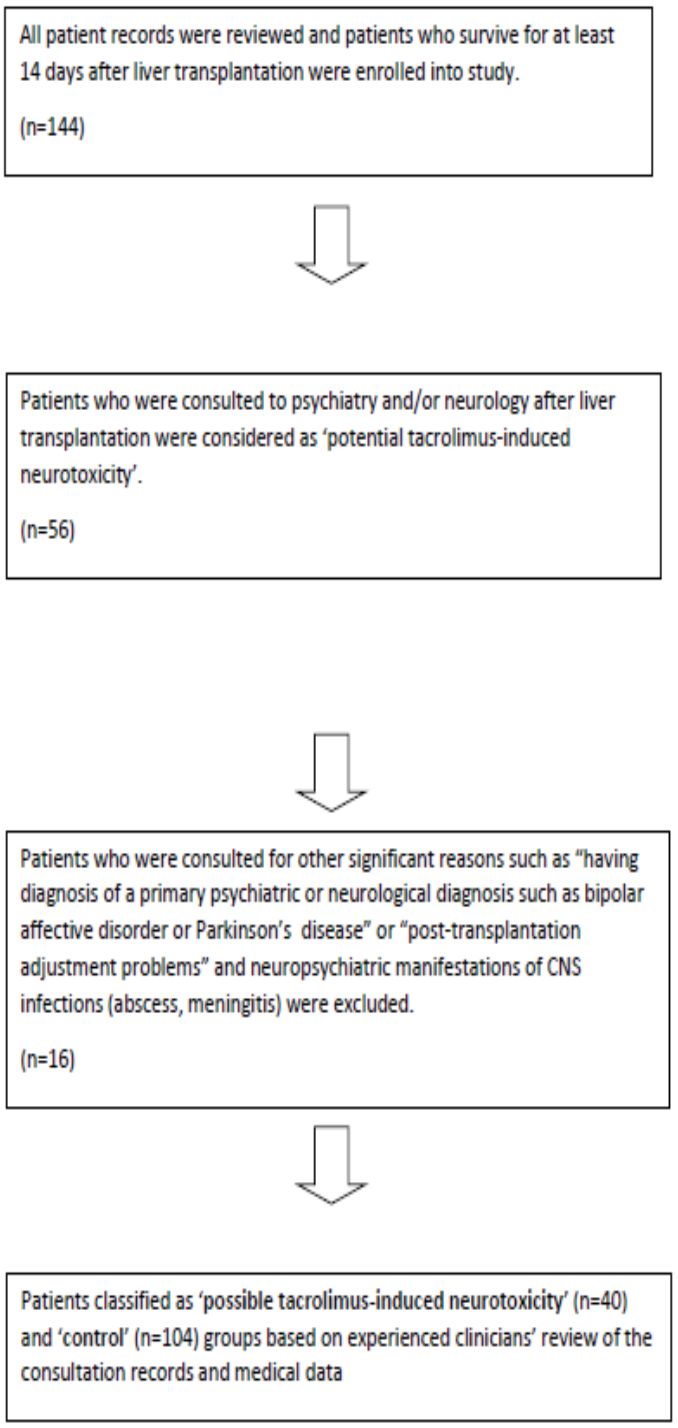

Figure 1. Flow chart of study design

DISCUSSION

Association between tacrolimus blood levels and tacrolimus-induced neurotoxicity has been investigated in the literature, with inconclusive results (4,9,12). In our study; contrary to our hypothesis we found that lower tacrolimus levels were associated with higher TIN risk which requires further explanation. In this retrospective study, we found an incidence of 27.8% for possible tacrolimus-induced neurotoxicity which is in line with previous studies (13).

Unlike our results, previous studies identified some independent risk factors such as previous hepatic encephalopathy, psychiatric disorders, advanced age, higher MELD and Child-Pugh scores, post-transplantation metabolic alterations, etiology of liver disease and higher tacrolimus levels (2,10,14). These inconclusive results could be explained by reverse causality; namely clinicians dose titration protocol. Patients with low performance status and with worse general health condition may limit the clinicians dose titration upwards. Hence, patients may prone to the CNS adverse effects as a result of other health conditions apart from tacrolimus blood level could also be misdiagnosed with TIN. Also, low rates of alcoholic cirrhosis and high rates of live donor transplantation in our sample could interfere with TIN diagnosis (10,14,15). Live donor transplantation could be associated with relatively better biochemical status before transplantation; which in turn reduces the CNS vulnerability to TIN.

In our study, to address these issues we conducted correlation analyses. In correlation analyses only post-transplantation CRP and pre-transplantation Hb levels were significantly correlated with tacrolimus blood levels which in turn could limit the reverse causality; again shed light on CNS vulnerability hypothesis (10). Increased CRP levels reflect inflammatory process which prone CNS to TIN. If the clinical decisions were solely be considered as an explanation, then post-transplantation creatinine levels should be correlated with tacrolimus blood levels. On the other hand, hypertensive patients blood tacrolimus levels were found to be significantly lower which is a finding possibly reflecting clinical decisions. No statistically significant difference was found between other groups (diabetes mellitus, previous encephalopathy, cadaveric/ live organ transplantation).

Pre-transplantation CRP levels positively and tacrolimus blood levels negatively significantly predicted the TIN which is a key finding of our study. Other variables such as age, gender, previous encephalopathy, cadaveric/ live donor transplantation and MELD score were not significantly added to the regression model. Significance of pre-transplantation CRP levels may be related with an inflammatory process mentioned above. Also, higher preoperative CRP are also related with poor outcomes in liver transplantation (16,17). While the explanation of significance of pre-operative CRP could be reasonable, it is difficult to say it for tacrolimus. In spite of the fact that calcineurin inhibitors are considered neurotoxic, there is no evidence on higher blood concentrations of tacrolimus mean higher neurotoxicity risk. Moreover, in our study tacrolimus blood level were negatively correlated with possible neurotoxicity. This interesting finding requires further explanation. An explanation might be unstandardized approach to diagnosis of TIN. To diagnose TIN, after switching tacrolimus neurotoxic symptoms must disappear in time however the information was lacking with this respect in previous studies (10,14); therefore we recommend to use 'possible TIN' term. Although our methodology couldn't allow to infer clear conclusions;

we speculate that, in therapeutic blood levels tacrolimus could be free (or relatively low) of neurotoxicity and on the other hand ineffective immunosuppressant therapy due to lower tacrolimus blood levels may potentially prone CNS to graft-related immune reactions.

In a few study age was suggested as a risk factor for TIN and degeneration of blood brain barriers and neurodegenerative changes due to aging was hypothesized (2,10,14). When we reviewed these papers it took our attention that patients in these samples were older than our sample; which could be an explanation.

A regression analysis with a model post-transplantation sodium, potassium levels and tacrolimus blood levels were also significantly predicted the possible TIN. However, only post-transplantation lower potassium levels were significantly added to the model. Lower post-transplantation potassium levels could reflect unexplained portion of variance- related variables (such as GIS disorders), which should be subject of further research.

Our study has some important limitations. First and major limitation of our study is its retrospective design and classification of patients with TIN according to the chart reviews. Secondly, most of the patients' TIN diagnosis were not proofed so we suggested to use diagnostic term 'possible TIN'. Apart from our study, because the diagnosis of TIN solely depends on clinical judgement with a huge range of symptoms such as tremor to hallucinations and the diagnosis requires the cessation or dose reduction of the agent which couples with clinical improvement. Because TIN diagnosis will lead to change of immunosuppressive treatment regimen; than more clear diagnostic criteria should be considered. Third, post-transplantation variables were with high rates of missing values which reduces the power of the analyses. We used tacrolimus blood levels of first two weeks. Although there is no consensus of time interval for TIN, researches indicated that TIN was more common in first weeks of starting tacrolimus. Owing to tacrolimus blood levels of first two weeks were well-monitored; we used first two weeks' levels. This was another limitation for our research.

Our study also has some strength features. In order to compare different tacrolimus mean blood values of patients with different index days; we create z-scores for each subject and enrolled into analysis with that value. This is important, because previous studies use variables such as minimum or mean tacrolimus blood levels without consideration of the index day which could clearly interfere with analyses. Secondly, we review all the patients' charts and records manually with two experienced liaison psychiatrists blind to each other; than if they reached a consensus for the diagnosis patient classified as possible TIN.

CONCLUSION

To our knowledge, this is the first study that shows an inverse association with tacrolimus blood levels and TIN. It is obvious that further well designed, prospective studies are needed to clearly establish risk factors.

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