ORIGINAL ARTICLE

Studying Calcineurin Inhibitors Metabolic Complications in Egyptian Liver Transplant Patients-A Single Center Trial

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Abstract

Background: Calcineurin inhibitors (CNIs) (Tacrolimus and cyclosporine [CSA]) are immunosuppressive drugs that are administrated to prevent liver rejection after liver transplantation. Their use has led to a reduced prevalence of acute rejection and improved transplant survival. However, their use is associated with many complications, these complications include hyperkalemia nephrotoxicity, hypertension (HTN), and new-onset diabetes mellitus (NODM). This study aimed to detect the incidence of CNIs complications in Egyptian patients after liver transplantation. **Study Design:** A retrospective evaluation with descriptive analysis study. **Patients:** All adults admitted for liver transplantation from 2008 to 2016 were included in this study. **Setting:** The study was conducted in the Liver Transplantation Unit, Ain Shams specialized hospital, Cairo, Egypt. **Results:** A total of 196 patients' medical files were retrospectively reviewed to detect the incidence of CNIs complications. The tacrolimus group included 86 patients and the cyclosporin group included 92 patients. The prevalence of developing HTN was lower in the cyclosporin group as only 25% of patients developed HTN versus 40% in the tacrolimus group. The prevalence of NODM in the tacrolimus group was higher in the CSA group (33% vs. 16%). The prevalence of hyperkalemia was 52% and 28% in group tacrolimus and cyclosporin groups, respectively. The rate of nephrotoxicity in the tacrolimus group was 60% versus 48% in the cyclosporin group. **Conclusions:** These findings may help guide physicians in their choice of immunosuppression and underscore the need for long-term follow-up for blood sugar and potassium levels, blood pressure, and kidney function tests.

Key words: Calcineurin inhibitors, Cyclosporine, Egypt, Liver transplant, Metabolic complications, Tacrolimus

INTRODUCTION

Calcineurin inhibitors (CNIs) are very effective and selective immunosuppressive medications. These medications inhibit the IL-2 gene transcription, by blocking the proliferation of lymphocytes after antigenic exposure. CNIs usage succeeded in reducing the incidence of transplantation comorbidities due to increasing patients and graft survival rates.[1] Tacrolimus (TAC) and Cyclosporine (CSA) are the main CNIs currently available for organ transplantation, both have patients' and grafts survival rates in heart transplantation,[2] liver,[3] and kidney.[4] The rates of acute organs transplantation rejection were very low after TAC-use[5] The incidence of hyperlipidaemia and hypertension (HTN) was also reduced after TAC-use.[6] The major dose and efficacy limiting adverse event associated with CNIs is nephrotoxicity. It may reduce their overall benefits for long-term graft survival.[7] CSA is more nephrotoxic than TAC as documented by various studies.[8] The induction of nephrotoxicity associated with TAC and CSA-use was not related to elevated blood trough levels.[9] It is very common

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that patients treated with CSA may develop renal impairment, even in those renal transplant patients who are perceived to be doing well under CSA immunosuppression. Both CSA and TAC cause acute and chronic nephrotoxicity.[10] Acute nephrotoxicity is reversible and appears to be related to the dosage of CSA or TAC. It is caused by a reduction in renal blood flow related to afferent arteriolar vasoconstriction. Chronic nephrotoxicity is irreversible interstitial fibrosis that develops in some patients after approximately 6–12 months of drug therapy. The latter is the major limitation on the use of these drugs because patients who develop chronic nephrotoxicity can progress to end stage renal disease. TAC has a direct glomeruloconstrictive effect, reducing renal perfusion and glomerular flow. Recipients of TAC may develop acute nephrotoxicity. Even patients on a low-dose TAC-based regimen develop nephrotoxicity.[9] Monitoring of serum creatinine and CNIs levels and adjusting the doses are crucial.

The clinical data showed a decrease in serum level of creatinine in the first 6 months after CNIs use.[11] Distal renal tubular acidosis (RTA) is one of several types of nephrotoxicity induced by tacrolimus treatment, resulting from inhibition of potassium secretion in the collecting duct.[12]

Distal renal tubular is a rare condition associated with tacrolimus treatment after liver transplantation. Hyperkalemia is the main sign of RTA.[13] This tacrolimus-induced RTA occurs in the absence of renal insufficiency, due to decreased renal tubular hydrogen ion secretion.

Tacrolimus use leads to Type IV RTA by reducing the activity of the Na+/K+ ATPase as well as the Na+/K+/2CL− cotransporter. These changes prevent the kidney from maintaining the normal electrochemical gradient, reducing urinary potassium and hydrogen ion secretion. Tacrolimus-related hyperkalemia RTA is the consequence of a tubular defect in potassium secretion induced by two major mechanisms. One is dose-dependent inhibition of Na+/K+-ATPase activity, and the other is aldosterone resistance secondary to a down-regulation of mineralocorticoid receptor expression.

The pathogenesis of metabolic acidosis is caused by hyperkalemia-induced impairment of NH_4^+ excretion.[14] New-onset diabetes mellitus (NODM) is increasingly recognized as a serious complication of organ transplantation. A recent analysis of the United States Renal Data System showed a markedly increased incidence of diabetes mellitus in CNI-treated renal transplant patients (n = 6943) following transplantation.[15] NODM results in increased susceptibility to infectious and cardiovascular complications may lead to diminished long-term graft survival and has a major impact on the quality and quantity of life.[16] NODM rates as high as 46% were reported before the introduction of CSA, largely related to the use of high-dose steroid immunosuppression required to prevent graft rejection.[17] The introduction of CSA allowed the use of lower steroid doses, and NODM rates declined to between 3% and 14%.[18] HTN frequently occurs early after liver transplantation when immunosuppression with CSA plus prednisone is used, amounting to a prevalence of 75–85% by 24 months.[19] Several reports have suggested that the incidence of HTN in patients treated with tacrolimus is lower than that in patients treated with CSA within the 1st year or two after kidney transplantation,[20] up to 3 years after heart transplantation,[17] and during the 1st year after liver transplantation.[21,22] Hepatitis C virus is the most common indication for liver transplantation. Studies showed that liver transplant recipients with Hepatitis-C virus require significantly lower oral doses of tacrolimus to achieve the same blood levels compared to non-Hepatitis-C virus patients. When taken orally, tacrolimus is absorbed into enterocytes and metabolized by intestinal cytochrome P450 (CYP450). The higher systemic levels of tacrolimus may be due to one or more of the following mechanisms; increased intestinal absorption decreased intestinal CYP450 metabolism or decreased intestinal enhanced by hepatitis C.[23] In the hepatitis C patient; the reduced tacrolimus dose and elevated level/dose ratio occurred at about the same time as the increase in ALT. That shows indirect evidence that as hepatic inflammation from recurrent hepatitis C increases, the clearance of tacrolimus decreases. Researchers have found that tacrolimus level increases in patients with hepatic dysfunction; it is mostly based on patients with rapid progressed hepatic failure. That is why the oral dose of tacrolimus should be adjusted and substantially reduced to maintain appropriate levels.[24] Tacrolimus is metabolized by hepatic CYP450 3A enzymes, in particular, CYP3A4 and CYP3A5. There is a lot of tacrolimus-drug interaction, which may increase the metabolism of tacrolimus and decrease its levels in the blood or decrease the metabolism of tacrolimus and increase its level in the blood so dose adjustment should be considered in the case of tacrolimus-drug interaction.[25] This study aimed to test the hypothesis of whether CNIs may induce arterial HTN, new-onset diabetes, renal dysfunction, or hyperkalemia in first liver transplant patients, as a secondary objective, the study will determine the factors that may affect tacrolimus serum levels such as hepatitis C virus and tarolimus-drug interactions.

MATERIALS AND METHODS

Study design

A retrospective evaluation with descriptive analysis study.

Patients

All adults admitted for liver transplantation from 2008 to 2016 were included in this study. Patients follow-up sheets, discharge reports, and mortality reports were reviewed for all the patients.

Exclusion criteria

The following patients were excluded from the study:
1. Patients with HTN before transplantation
2. Patients with diabetes mellitus before transplantation
3. Patients with impaired kidney functions before transplantation
4. Patients with hyperkalemia before transplantation.

Setting

This study was conducted in the Liver Transplantation Unit, Ain Shams specialized hospital.

All patients' files were reviewed to record the tacrolimus doses and serum levels.

Monitoring for HTN induction after liver transplantation

All patients' data were analyzed and any blood pressure (BP) elevation (>140/90) or starting any new antihypertensive medication after liver transplantation was recorded to detect the prevalence of HTN induction post-liver transplantation.

Monitoring for diabetes mellitus induction after liver transplantation

All patient's data were analyzed and blood sugar levels (fasting glucose, Hemoglobin A1C) were recorded to detect the prevalence of diabetes mellitus induction post-liver transplantation.

Monitoring for hyperkalemia and renal dysfunction after liver transplantation

Uric acid, BUN, serum creatinine, and serum potassium (K+) level together with trough level of tacrolimus were recorded for all patients to detect the prevalence of renal dysfunction or hyperkalemia induction post-liver transplantation.

Doses and serum levels: Group I (Tacrolimus group): All patients received a dose of 0.1–0.15 mg/kg/day BID after liver transplantation to achieve a serum level of 5–20 ng/ml.

Group II (Cyclosporin group): All patients received a dose of 15 mg/kg/day BID after liver transplantation, then the dose was reduced to 5–10 mg/kg/day BID to achieve a serum level of 100–300 ng/ml.

The relationship between hepatitis C virus and tacrolimus blood levels was done by comparing the serum levels of tacrolimus in hepatitis C virus and non-hepatitis C virus liver transplantation recipients. Tacrolimus-drug interactions were detected and the effect of this interaction on tacrolimus serum level was monitored and recorded.

RESULTS

A total of 196 patients' medical files were retrospectively analyzed to study CNIs (Tacrolimus and CSA) complications after liver transplantation. All patients admitted to the liver transplantation unit in Ain Shams specialized hospital during the period from 2008 to 2016 were included in this analysis. A total of 18 patients were excluded from the study analysis after reviewing their mortality reports. These patients died within the 1st month after transplantation, so their data were excluded during results interpretation. A total of three patients were excluded from the study analysis because they received.

Both drugs (Tacrolimus and CSA), so it was not possible to study the effect of a single drug on the studied complication.

The patients were divided into two groups:
Group I: Tacrolimus group (86 patients),
Group II: CSA group (92 patients).

The patient's age was ranged from 19 to 76 years, with a mean age of 50.3. Male patients were147 and female patients were 15 patients. Tables 1-4 shows blood, liver functions, kidney functions, and electrolytes and glucose levels measurements after liver transplantation.

Figure 1 shows the prevalence of CIs metabolic complications detected in both groups.

Tacrolimus-drug interactions were detected using Medscape-drug interaction checker and a total of four types of drug interactions were detected as shown in Table 5. The serum levels of tacrolimus in hepatitis C virus and non-hepatitis C virus liver transplantation recipients were compared as shown in Table 6 using Student's *t*-test and the difference between tacrolimus serum levels was statistically significant only after 3 months of transplantation.

DISCUSSION

A total of 196 patients were enrolled in this study, Tables 1-4 show blood, liver functions, kidney functions, and electrolytes and glucose levels measurements after liver transplantation. The prevalence of developing HTN post-liver transplantation was one of our primary objectives.

All patient's data were analyzed and any BP elevation (>140/90) or starting any new antihypertensive medication after liver transplantation was recorded to detect the prevalence of HTN induction post-liver transplantation. A total of 34 and 23 cases developed HTN after tacrolimus use and cyclosporin use, respectively. About 40% of the patients in the Tacrolimus group developed HTN as shown in Figure 1. Our results were comparable with Boudjema and his colleagues who conducted a randomized control

Table 1: Blood measurements after liver transplantation

	Plt (L)	CRP (mg/L)	PT (Seconds)	INR	PTT (Seconds)
Mean	192.0833	9.600833	27.96667	2.0625	93.61667
St. Dev.	184.3023	14.77457	18.65741	1.72396	90.41474
Median	176	2.5	16.45	1.06	72

Table 2: Liver function measurements after liver transplantation

	T. Bil. (micromole/L)	D. Bil. (micromole/L)	AST (IU/L)	ALT (IU/L)	ALK. Ph (IU/L)	GGT (IU/L)
Mean	2.775	4.204167	248.1083	327.8417	118.9583	107.1667
St. Dev.	2.701557	5.572924	274.9899	351.0012	125.5194	116.1236
Median	1.55	0.9	168	265	65	65.5

Table 3: Kidney function measurements after liver transplantation

	T. Prt. (g/dL)	Alb. (g/dL)	BUN (mg/dL)	Sr. Creat. (mg/dL)	Uric acid (mg/dL)
Mean	7.25	4.125	49.75	4.341667	5.433333
St. Dev.	3.348134	3.049627	59.02715	6.839652	4.124722
Median	7.05	3.75	14.5	1.8	5.75

Table 4: Electrolytes and blood glucose measurements after liver transplantation

	Na (micromole/L)	K (micromole/L)	Ca (micromole/L)	Po4 (micromole/L)	glucose level (micromole/L)
Mean	129.75	4.1	5.283333	3.375833	105.8333
St. Dev.	21.11064	2.205778	4.286943	2.678627	21.69255
Median	134.5	3.8	6.85	2.65	103

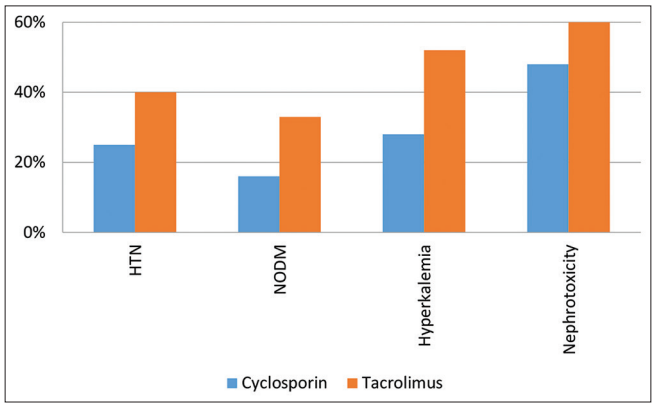

Figure 1: The prevalence of CIs metabolic complications

study to detect the incidence of developing HTN after using tacrolimus post-liver transplantation and concluded that in most transplant patients, arterial pressure usually increases to a hypertensive level as about 46% of patients developed HTN.[26] The prevalence of developing HTN was lower in Group II (the Cyclosporin group) as only 25% of patients developed HTN versus 40% in the tacrolimus group. Another study was conducted by Vincent and his colleagues to monitor the BP status of patients treated with CSA and those treated with tacrolimus and compare the prevalence of HTN 24 months after liver. This study concluded that the prevalence of HTN in the CSA and tacrolimus groups was 82% and 64%, respectively.[27]

New-onset diabetes after transplantation (NODAT) is a frequent metabolic complication and is considered a risk factor for patients undergoing a liver transplant.[28] In this present study, all patient's data were analyzed to record the blood sugar levels (fasting glucose, Hemoglobin A1C) and to detect the prevalence of diabetes mellitus induction post-liver transplantation. The prevalence of NODAT in Group I 33%. This rate was comparable with the findings of another large-scale retrospective study which reported a cumulative incidence of NODAT of 24% at 36-month post-renal transplantation with tacrolimus use.[29] The prevalence of NODAT in Group I (tacrolimus group) was higher than in the CSA group (33% versus 16%). Our results were comparable with the results of Moro and his colleagues who concluded that tacrolimus-treated patients had significantly higher rates of NODAT (7, 17, and 15%) compared with CSA-treated patients (2, 9, and 7%); $P = 0.015$.[30] A meta-analysis of 16 randomized trials also reported a significantly higher incidence of NODAT in patients receiving TAC than with CSA (10.4% vs. 4.5%) after solid organ transplantation.[1] Potassium levels were recorded for all patients to detect the prevalence of hyperkalemia post-liver transplantation in both groups.

Table 5: Tacrolimus-drug interactions and tacrolimus serum levels

Interacting drugs	Mechanism of interactions	Type of interaction according to Medscape interaction checker/ (number [%])	Action needed	Mean Tacrolimus serum level +/−SD
Amikacin	Amikacin and tacrolimus both increase nephrotoxicity and/or ototoxicity	Serious/(5 [1.7])	Avoid or use alternate drug	6.3 +/−2.06
Mycophenolate	Mycophenolate and tacrolimus both increase immunosuppressive effects; risk of infection/Avoid or Use Alternate Drug	Serious/(62 [21])	Avoid or Use Alternate Drug	7.68+/−2.90
Pantoprazole	Pantoprazole will increase the level or effect of tacrolimus by affecting hepatic enzyme CYP2C19 metabolism	Significant/(56 [19])	Use Caution/ Monitor	6.9+/−2.14
Metronidazole	Metronidazole will increase the level or effect of tacrolimus by affecting hepatic/ intestinal enzyme CYP3A4 metabolism.	Significant/(58 [20])	Use Caution/ Monitor.	6.2+/−2.02
Methylprednisolone	Methylprednisolone will decrease the level or effect of tacrolimus by affecting hepatic/intestinal enzyme CYP3A4 metabolism.	Significant/(9 [3])	Use Caution/ Monitor	6.6+/−2.08
Amlodipine	Amlodipine will increase the level or effect of tacrolimus by unspecified interaction mechanism.	Significant/(9 [3])	Modify Therapy/ Monitor Closely. Adjust dose when appropriate	6.7+/−2.14
Esomeprazole	Esomeprazole will increase the level or effect of tacrolimus by affecting hepatic enzyme CYP2C19 metabolism.	Significant/(34 [11.5])	Use Caution/ Monitor.	6.3 +/−2.96
Fluconazole	Fluconazole will increase the level or effect of tacrolimus by affecting hepatic/ intestinal enzyme CYP3A4 metabolism.	Significant/(3 [1])	Use Caution/ Monitor	6.7+/−2.04
Prednisone	Prednisone will decrease the level or effect of tacrolimus by affecting hepatic/ intestinal enzyme CYP3A4 metabolism.	Significant/(59 [20])	Use Caution/ Monitor	6.3 +/−2.96

Table 6: Tacrolimus serum levels in HCV and non-HCV patients post-liver transplantation

	HCV Patients after 3 months	Non-HCV Patients after 3 months	HCV Patients after 1 year	Non- HCV Patients 1 year	HCV Patients after 2 years	Non- HCV Patients after 2 years
Mean	6.02219	6.1724409	6.2825776	6.724138	6.054645	7.511765
St. Dev.	3.524896	3.0814519	3.453908	2.958723	3.214881	3.535513
P. Value (Student's *t*-test), Significant <0.01	0.032252*		0.064967*		0.179998*	

*not significant

The prevalence of hyperkalemia was 52 % and 28% in Groups I and II, respectively.

Tacrolimus was associated with a higher incidence of hyperkalemia than CSA.

The same findings were obtained by Jones and his colleagues who concluded a study on CNIs (CSA and tacrolimus) and concluded that CNIs have long been known to cause electrolyte abnormalities including hyperkalemia and hypernatremia, with higher incidence with tacrolimus. Serious complications may occur due to CNI-induced electrolyte abnormalities, including one death reported due to CSA-induced hyperkalemia.[31] The CNIs cyclosporin A (CSA) and tacrolimus (FK506) are associated with dose-and efficacy limiting adverse events, including nephrotoxicity, which may diminish their overall benefits for long-term graft survival.[7]

A total of 51 cases developed nephrotoxicity during tacrolimus use. The rate of nephrotoxicity in the tacrolimus group was 60%, while 44 cases developed nephrotoxicity during CSA use. The rate of nephrotoxicity in the CSA group was 48%.

The prevalence of nephrotoxicity in the tacrolimus group was higher than in the CSA group. Table 5 shows tacrolimus-drug interactions and tacrolimus serum levels. During the study period, a total of 295 tacrolimus-drug interactions were recorded, 23% were serious, 77% were significant, but none of these interactions affected tacrolimus serum levels. The trough tacrolimus serum levels were at the recommended range in all patients. The effect of HCV on tacrolimus serum levels was also studied, Table 6 shows tacrolimus serum levels in HCV and NON-HCV patients post-liver transplantation after 3 months, 1, and 2 years' post-liver transplantation. The difference in means of tacrolimus serum levels was not statistically significant in all durations. On the contrary, another study conducted by Trotter and colleagues,[32] concluded that the levels of tacrolimus in HCV and non-HCV virus patients were not significantly different in all intervals, except month 9. The HCV recurrence rates were recorded in this present study. About 9.2% and 2.17% of patients developed HCV recurrence after liver transplantation in Groups I and II, respectively. The incidence of HCV recurrence/survival rates was also studied by Martin and his colleagues who conducted a two-arm randomized study on 79 patients to receive tacrolimus or CSA as primary immunosuppressant post-transplantation. Their results reviled that a month 12 cumulative probabilities of histological hepatitis C recurrence for tacrolimus and CSA-treated patients were 38% and 54 % ($P = 0.19$), no significant differences were observed between the two treatment arms in histologically-diagnosed HCV recurrence/survival rates and the choice of CNIs does not impact the severity of recurrent HCV.[33]

CONCLUSIONS

These preliminary findings underscore the need for long-term follow-up of the two immunosuppressive agents and, preferably, the use of sensitive markers of renal function. In addition, our results suggest a role for therapeutic strategies to reverse or ameliorate these adverse changes associated with HTN. These strategies could include the prevention of obesity after tacrolimus and CSA use and perhaps clinical trials with angiotensin-converting enzyme inhibitors or other drugs to minimize progressive renal insufficiency in tacrolimus-treated liver-transplant recipients. These findings may help guide physicians in their choice of immunosuppression and underscore the need for long-term follow-up for blood sugar and potassium levels, BP, and kidney function tests. CNIs' metabolic complications may be affected by a certain genetic polymorphism in Egyptian patients. Further studies should be conducted to study the effect of CNIs' genetic polymorphisms in the Egyptian population.

ETHICAL APPROVAL

The study was approved initially by the Ethics Committee for graduation projects, Faculty of Pharmacy - the British University in Egypt then the study proposal was revaluated and approved also by the Ethics Committee of Faculty of Pharmacy – Egyptian Russian University (Reference No. ECH-015).

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