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Cyclosporine Toxicity and Toxicokinetics Profiles in Renal Transplant Recipients

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Abstract

Background: Cyclosporine is the backbone of immunosuppression in kidney transplantation. However, it leads to multiple toxic effects, most of which are dose-dependent. In this respect, the quality of renal functions is undoubtedly linked to cyclosporine drug levels.

Objective: To evaluate the association among cyclosporine trough-peak levels, dosage and its toxic effects.

Methods and materials: In 102 kidney transplant recipients, serum cyclosporine trough-peak levels, serum creatinine, blood urea, blood urea and nitrogen, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase were measured periodically from the beginning of May, 2011 until the end of July, 2012.

The relationships among previous laboratory parameters were detected in relation to the prevalence of toxic cyclosporine effects.

Results: Consequently, the patients are with renal transplantations; concentrations of cyclosporine trough that can get lowered safely towards the range of 150-200 ng/ml, added by minimal toxic cyclosporine effects without increased risk for graft rejection.

Conclusion: The findings of this study showed the detrimental toxic effects of high cyclosporine concentrations and the efficiency of low cyclosporine trough/peak levels in maintaining of an efficient immunosuppressive effect plus a minimal toxic cyclosporine effects and positive therapeutic outcomes in the renal transplant patients.

Keywords: Renal transplant patients; Cyclosporine toxicity; Immunosuppression therapy

Introduction

Cyclosporine is used for immunosuppression following organ transplantation and for treatment of autoimmune disorders. Cyclosporine formulations are available for oral, parenteral, rectal, ophthalmic and pulmonary aerosol administration. Repeated therapeutic ingestion may produce toxicity when trough serum levels exceed 300 ng/ml. Cyclosporine causes immunosuppression by suppressing helper T-lymphocytes release of lymphokines [1].

There is the function related to the impaired renal aspects under major mode of long-term complications that are noted after the instance of organ transplantation under cyclosporine era, added by accepted notions that remain unavoidable towards the toxic effect in relation with the standard immune suppression. Definite as well as reproducible mode of cross-correlation get noted for levels of cyclosporine blood status, manifestations of toxin and functionalities of renal context [2].

By means of overseeing the process of maintaining immune suppressants are followed by kidney transplantation that usually leaves the physicians about their walking over tightrope, and the attempt to attain precise balance among the respective content. Failure to maintain sufficient doses of immunosuppressive agents can lead to acute rejection, chronic allograft nephropathy, and graft loss. There is excess mode of immune suppression that never heightens risk towards drug-specific that is related to the toxic complications, and further leaves patient vulnerable that is related to the opportunistic infections as well as malignancy. There is a narrow therapeutic index in relation with some immune suppressants that has potentiality for interactions of drugs, poor correlation among dose as well as whole blood concentrations are such that the management of Cyclosporine turns increasingly complicated [3].

Toxicity related to the long-term immune suppressive is a sort of therapy that remains as a paramount towards long-term aspects in terms of renal transplantation. Here the quality of renal function remains undoubtedly connected towards cyclosporine levels of drug. In reference to renal transplantation, there is determined cyclosporine mode of trough levels with historical modes related to the maintenance among 150 as well as 300 ng/ml under various therapeutic drug-monitoring centers, that is without direct evidence with the demand for high levels with vulnerability towards the production of toxic effects, whereas there is the application of multiple mode of drug Immune suppression therapy [4].

Primarily, the exceeding mode of higher cyclosporine dosage should be from 16 to 18 mg/kg/day [5] must get reduced drastically with huge organ recipients with major failure in the toxic renal function [6]. Currently, there are dosages meant for cyclosporine towards 6 to 10 mg/kg/day [4], yet can offer acute/long-term cyclosporine that is subject to induce toxic manifestations as well as deterioration of the renal function, that are there with majority patients with multiple-drug immune suppression followed by renal transplantation [7].

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Though the therapeutic monitoring of drug get started for a long term in Saudi Arabia (1984), with least studies, particularly on cyclosporine toxicity that has got transplant patients, performed as per this service [8,9]. Therapeutic monitoring services of drug are for immune suppressant drugs that are implied for identification of optimum concentration of the serum without toxic/sub therapeutic manifestations. The Cyclosporine remains without concentration in the process of monitoring with potentiality towards life threatening toxicities, particularly in terms of organ transplantation where the therapy remains life sustaining [10].

Levels of Cyclosporine (that are trough and peak) monitor routine approaches within Dammam Regional Poison Control Center (DRPCC). Thus, the objective of this research is to see the relationship among the levels of Cyclosporine, dosage as well as toxic effects through the studied renal transplantation in first 15 months followed by the process of transplantation.

Methods and Material

Study of the setting

Observational retrospective has been noted through the cohort design for respective research. Total of 522 toxicokinetic added by pharmacokinetic and determined profiles attained from 102 patients experiencing kidney transplantation, and having immune suppression therapy through cyclosporine plus that is a Steroid therapy as well as a combination with Azathiorporine therapy from the beginning of May, 2011 until the end of July, 2012. These are the toxicokinetic and pharmacokinetic mode of profiles classified under seven groups noted in the post-transplant phases.

Criteria as inclusion as well as exclusion

Inclusion criteria are those mopeds that are noted for kidney transplantation with oral formulation "modified form" noted for the cyclosporine round twice daily, between 18 years of age and above, with information in relevance to the level of Cyclosporine trough (C0) with/without cyclosporine peak or for the instance of 2 hrs post dose (C2). Allograft gets attained from living/cadaveric donors. The patients noted for kidney transplantation without receiving cyclosporine or cyclosporine therapy get meant for other rather than the renal transplantation with less age group than 18 years with severe heart failure, hepatic failure, hypertension, drug protocols with the inclusion of polyclonal/monoclonal antibodies, effects of drugs over the level of cyclosporine "as Erythromycin, Metclopraminde, Cimetidine, Ciprofloxacin, Ketoconazole, Non-steroidal anti-inflammatory and Oral Contraceptive Pills", problems of urology, a history of acute rejection in the 1st week after transplantation, and those without above declared data get excluded from determined study.

Parameters for the study of population

Data was collected from patients who underwent the renal transplantation electronic records at Dammam Regional Poison Control Center DRPCC-KSA. Data collected from patients electronic records from medical domain are inclusive of demographic data, span of post-transplant phase, type of donor for the transplanted kidney, immune suppressant, mode of therapy, cyclosporine's dose, which are reported as the toxic symptoms added by the serum creatinine, signs, or the levels of Cyclosporine trough peak therapy, Blood Urea or Nitrogen level, level of Blood Urea, Serum Glutamic Oxaloacetic Transaminase Enzyme, Serum Glutamic Pyruvic Transaminase Enzyme and Level of Serum Albumin.

Cyclosporine standard protocol

Cyclosporine was ordered frequently at the start of therapy, basis when trying to establish a dosing regimen. Once an appropriate dose has been determined, the level was tested less frequently and once every 1-3 months according to the current patient condition. The target blood cyclosporine trough-peak was (level from 150 to 200 ng/ml trough per 700 to 800 ng/ml peak) within the transplantation operation of the renal related patients and all over the postoperative transplantation course.

Grouping meant for the studied patients

Cases under the division of 7 groups as per interval of post-transplantation as follows:

Group I: patients who are having post-transplantation phase less or more than 1 month.

Group II: patients who are having post-transplantation phase from 2 to less than 4 month.

Group III: patients who are having post-transplantation phase from 4 to less than 6 month.

Group IV: patients who are having post-transplantation phase from 6 to less than 8 month.

Group V: patients who are having post-transplantation phase from 8 to less than 10 month.

Group VI: patients who are having post-transplantation phase from 10 to less than 12 month.

Group VII: patients who are having post-transplantation phase more than 12 month.

Records review process of the electronic medical

Three reviewers conducted the entire review process–'pharmacists'. Taking the help of individual patient records, the individual patient records were accessed by way of medical record number access into the electronic-medical records. Standardized Excel sheet has got predefined information placed over password that has been protected as per the share-drive added by reviewer towards the entrance of the abstracted data. Each of the patients got independent review through 2 researchers with separately completed worksheets, which are further reviewed for the state of agreement, and any identified discrepancies were reconciled by a third reviewer, who conducted an independent review. There was complete agreement between data extractors.

Procedure of the assay

Therapeutic Drug Monitoring Department, DRPCC investigates drugs through the application of Abbott AXSYM. Samples of blood are all taken prior and 2 hours after the morning cyclosporine dose.

Statistical mode of analysis

There was a statistical analysis of the entire data with the help of the present SPSS statistical package Version 19. This data was further presented as mean ± Standard Deviation of Means (S.D.M). There was also a comparison exercise done between the two groups that was carried out with the help of t-test and p value was considered statistically significant if <0.05.

Results

Current work has got 102 patients (with 64 male participants and 38 female participants with mean age ± SD: 43.46 ± 12.9 years). Total

levels of blood cyclosporine samples were 522 in the entire 15-month study period. (With 289 samples of blood for trough as well as peak levels–233 samples of blood were for just the trough level).

Table 1 is subject to demonstrate features of studied patients as per sex, age, nationality, mean weight of the body, mean mass index of the body, type of donor, mean dose of cyclosporine, associated level of mean serum of creatinine and clearance of creatinine. Moreover, the same represent classification related to the studied cases within 7 groups as per post-transplant time span. First group has got renal transplant of the receipt patients within a month from the process of transplantation till seventh group with renal recipients of transplantation that is more than 12 months from the date of transplantation.

Patients' demographic data (n=102)			
Parameter			Value
Age (Years) (Mean ± SD)			43.46 ± 12.9
Sex (Male/Female)			(64/38)
Race (Saudi/Non-Saudi)			(85/17)
Body Weight (kg) (Mean ± SD)			72.8 ± 24.8
Body Mass Index (Mean ± SD)			28.8 ± 8.4
Donor type (Living Unrelated Donor/Cadaveric Unrelated Donor)			(101/1)
Cyclosporine dose (mg/Kg) (Mean ± SD)			2.5 ± 1.1
Cyclosporine dose (mg/day) (Mean ± SD) [In two divided dose]			176.5 ± 60.9
Serum Creatinine Level (mg/L) (Mean ± SD)			1.3 ± 0.9
Creatinine Clearance (ml/min) (Mean ± SD)			89.1 ± 50.8
Frequencies/percentages of referral cyclosporine blood samples (n=522)			
	Patients No	Referral blood samples	
Groups		Frequency	Percentage%
Group I (1 month)	69	89	17
Group II (2-4 months)	75	83	16
Group III (4 -6 months)	65	87	16.6
Group IV (6-8 months)	67	63	12
Group V (8-10 months)	59	71	13.6
Group VI (10-12 months)	54	61	11.6
Group VII (>12 months)	62	68	13.2
Total	102	522	100

Table 1: Demographic data of the patients with frequencies and percentages meant for referral cyclosporine samples of blood towards Dammam Regional Poison Control Center.

Groups	Percentage (No)					
	Subtherapeutic		Therapeutic		Toxic	
	Trough Level	Peak Level	Trough Level	Peak Level	Trough Level	Peak Level
Group I (1 month)	49.5(44)	65.5 (30)	43.8 (39)	13 (6)	6.7(6)	21(10)
Group II (2-4 months)	51.8 (43)	52 (21)	42.4 (35)	28 (11)	5.8(5)	20 (8)
Group III (4 -6 months)	46.2 (40)	54.3(19)	46.2(40)	16.3 (6)	7.6(7)	29.4 (10)
Group IV (6-8 months)	38.1 (24)	46.6 (15)	50.8 (32)	34.7 (11)	11.1(7)	18.7 (6)
Group V (8-10 months)	53.5 (38)	54.2 (13)	43.7 (31)	12.5 (3)	2.8 (2)	33.3 (8)
Group VI (10-12 months)	50.8 (30)	56.7 (17)	47.6 (29)	2 0 (6)	1.6 (2)	23.3 (7)
Group VII (>12 months)	45.6(31)	55.6 (15)	45.6 (31)	22.2 (6)	8.8 (6)	22.2 (5)

*289 referral blood samples for both trough and peak levels–233 referral blood samples for trough level only (total referral blood samples 522).

Table 2: Total percentages of cyclosporine levels in trough-peak as per diversified therapeutic range (n=522).

All reported cyclosporine concentrations (n=522)		
Groups	Range	Mean ± SD
K_e (hr^{-1})	0.03-0.9 (hr^{-1})	0.159 ± 0.061 (hr^{-1})
$t_{½}$ (hr)	0.77- 83.8 (hr)	5.1 ± 3.87 (hr)
V/F (L)	22.23-1819.7 (L)	129.79 ± 96.67 (L)
CL/F (L/hr)	5.15-48.93 (L/hr)	17.85 ± 5.9 (L/hr)
AUC (ng/ml/hr)	2348.5-14915.9 (ng/ml/hr)	9907.2 ± 818.23 (ng/ml/hr)
C_0: (ng/mL)	16-959.1 (ng/ml)	180.7 ± 112.6 (ng/ml)
C_2: (ng/mL)	110-1887.7 (ng/ml)	789.2 ± 355.6 (ng/ml)
Toxic cyclosporine concentrations (Trough level >300 ng/dl /Peak level>1000 ng/dl) (n=57)		
Groups	Range	Mean ± SD
Ke (hr^{-1})	0.06-0.17 (hr^{-1})	0.08 ± 0.035 (hr^{-1})*
$t_{½}$ (hr)	12.8- 83.8 (hr)	10.6 ± 7.34 (hr)**
V/F (L)	72.6-1819.7 (L)	260.29 ± 243.4 (L)*
CL/F (L/hr)	7.59-35.41 (L/hr)	18.66 ± 5.7 (L/hr)
AUC (ng/ml/hr)	5429.27-13575.6 (ng/ml/hr)	9836.1 ± 1010.61 (ng/ml/hr)
C_0: (ng/mL)	301.1-959.1 (ng/ml)	439.9 ± 232.7 (ng/ml)
C_2: (ng/mL)	725.2-1887.7 (ng/ml)	1007.6 ± 288.4 (ng/ml)
High normal cyclosporine concentration (Trough level 200-300ng/dl/Peak level 900-1000ng/dl) (n=125)		
Groups	Range	Mean ± SD
Ke (hr^{-1})	0.03-0.8 (hr^{-1})	0.18 ± 0.19 (hr^{-1})
$t_{½}$ (hr)	3.05-24.46(hr)	5.7 ± 1.9 (hr^{-1})
V/F (L)	44.39-441.22 (L/hr)	146.1 ± 62.5(L/hr)
CL/F (L/hr)	7.37-35.91 (L/hr)	17.96 ± 5.6 (L/hr)
AUC (ng/ml/hr)	8133.33-12192.9 (ng/ml/hr)	9933.42 ± 411.23 (ng/ml/hr)
C_0: (ng/mL)	200.5-298.2 (ng/ml)	243.13 ± 28.8 (ng/ml)
C_2: (ng/mL)	783.69-1767.6 (ng/ml)	912.1 ± 263.3 (ng/ml)
Normal cyclosporine concentration (Trough level 150-200/dl/Peak level 800-900 ng/dl) (n=151)		
Groups	Range	Mean ± SD
Ke (hr^{-1})	0.03 -1.3 (hr^{-1})	0.21 ± 0.2 (hr^{-1})
$t_{½}$ (hr)	3.31-21.65(hr)	4.9 ± 1.93 (hr^{-1})
V/F (L)	45.23-309.32 (L/hr)	125.27 ± 51.27(L/hr)
CL/F (L/hr)	7.17-34.46 (L/hr)	18.02 ± 6.1(L/hr)
AUC (ng/ml/hr)	5437.4-1083902 (ng/ml/hr)	9932.42 ± 448.94 (ng/ml/hr)
C_0:(ng/mL)	150.0-199.7.2 (ng/ml)	174.77 ± 15.38 (ng/ml)
C_2: (ng/mL)	411.1-1328.2(ng/ml)	783.8 ± 183.5 (ng/ml)
K_e: Elimination constant V: Volume of distribution F: Bioavailability CL: Clearance AUC: Area Under the Curve		C_0:Cyclosporine trough level C_2:Cyclosporine peak level *P<0.05% **P ≤ 0.01%

Table 3: Pharmacokinetic or toxicokinetic sort of parameters under patients with renal transplanted for the diversified concentration of cyclosporine.

Percentages as well as total levels of cyclosporine are being presented under Table 2. Level of Cyclosporine related to the trough level got classified under 3 determined categories; with sub therapeutic range being less than the 150 ng/ml, added by therapeutic range between 150 to 300 ng/ml added by toxic tough level with more than 300 ng/ml. Moreover, level of Cyclosporine peak got classified under three sectors; with sub therapeutic being less than 800 ng/ml, added by therapeutic range between 800 to 1000 ng/ml along with toxic range that remain more than 1000 ng/ml. There were 522 referral samples [289 (trough & peak) and 233(trough only)].

Pharmacokinetic or the Toxicokinetic (PKs or TKs) of Cyclosporine in is for kidney being transplanted by the patients under diversified level of cyclosporine concentrations with significant difference between toxic and normal cyclosporine concentrations as in Table 3.

Table 4 offers clarified effects of cyclosporine toxin frequencies as well as percentages under renal transplantation of recipients towards variable related to cyclosporine concentrations.

Daily dosage of Cyclosporine, derivations from laboratory are added by the diversified pharmacokinetic parameters that gets detected under different mode of post-transplanted sort of intervals that get presented under Table 5.

Statistical connection among diversified laboratory variables added by daily dosage of cyclosporine was reported towards Table 6. Diversified notions were marked under statistical significance among direct as well as inverse mode of statistical instances of cyclosporine dosage, peaks and trough cyclosporine level added by various structures of renal as well as hepatic pharmacokinetics aspects studied under renal transplantation (with p value <0.05).

Discussion

The current research considered 102 patients (of whom 64 are males and 38 are females with a determined mean age ± SD, 43.46 ± 12.9 year). Further, there is the investigation meant via 522 cyclosporine mode of monitoring blood samples for a span of 15 months. Levels of 57 cyclosporine were noted within toxic range of cyclosporine. In terms of clinical signs; instance of headache remain as the commonest toxic cyclosporine mode of clinical presentation; detected in terms of 66 numbers of monitoring cyclosporine samples of blood.

Introduction meant for cyclosporine within standard immune suppression protocol meant for patients followed by renal transplantation attained improved rate of survival that is significantly subject to decrease incidence as well as mortality in relation with rejection as well as infection. Still, prior old dosage are noted from 14 to 18 mg/kg/day that is implied within renal transplantation of recipients in terms of larger scale that gets manifestations over detrimental toxin like hypertension [11], instance of severe nephrotoxicity [12], added by increased mode of malignancy [13]. In order to reduce the cyclosporine doses, compound gets implemented as a part of combination in relation with prednisone as well as azathioprine, that permits dose reduction

Parameter	Group I	Group II	Group III	Group IV	Group V	Group VI	Group VII
	1 month	2-4 month	4-6 month	6-8 month	8-10 month	10-12 month	>12 month
All reported cyclosporine concentrations (n=522)							
No Signs of Toxicity	75	68	72	44	60	50	56
Hypertension	11	12	9	12	6	8	8
Tremors	1	2	---	2	1	---	2
Facial Flushing	—	1	3	2	1	—	1
Over growth of gums	—	—	—	1	3	—	1
Hirsutism	—	—	1	—	—	1	—
Visual Impairment	—	—	2	2	—	2	—
Toxic cyclosporine concentrations (Trough level >300 ng/dl and or Peak level >1000 ng/dl) (n=57)							
No Signs of Toxicity	5	4	2	—	—	1	—
Hypertension	7	6	7	7	4	6	3
Tremors	–	1	—	2	1	—	1
Facial Flushing	–	—	3	1	—	—	1
Over growth of gums	—	—	—	—	3	—	1
Hirsutism	—	—	1	—	—	1	—
Visual Impairment	—	—	2	2	—	1	—
High normal cyclosporine concentration (Trough level 200-300 ng/dl/Peak level 900-1000 ng/dl) (n=125)							
No Signs of Toxicity	29	17	31	23	17	20	26
Hypertension	3	4	—	4	1	1	4
Tremors	1	—	—	—	—	—	1
Facial Flushing	—	1	—	1	—	—	—
Over growth of gums	—	—	—	1	—	—	—
Hirsutism	—	—	—	—	—	—	—
Visual Impairment	—	—	—	—	—	1	—
Normal cyclosporine concentration (Trough level 150-200 ng/dl/Peak level 800-900 ng/dl) (n=151)							
No Signs of Toxicity	27	46	37	14	31	25	14
Hypertension	1	—	2	—	1	1	—
Tremors	—	1	—	—	—	—	—
Facial Flushing	—	—	—	—	1	—	—
Over growth of gums	—	—	—	—	—	—	—
Hirsutism	—	—	—	—	—	—	—
Visual Impairment	—	—	—	—	—	—	—

Number and percentage of studied cases regarding toxic cyclosporine signs (n=102)						
No Signs of Toxicity	Hypertension	Tremors	Facial Flushing	Gum Over growth	Hirsutism	Visual Impairment
84 (82.7%)	15 (14%)	11(10%)	5 (4%)	1(0.9)	1(0.9)	3(2.9%)
Toxic Cyclosporin (Cs) Level	11	8	4	1	1	2
High normal Cs Level	3	2	–	—	—	1
Normal Cs Level	1	1	1	—	—	—

Table 4: Effects of cyclosporine toxin frequencies within recipients of renal transplantation.

Parameter	Group I	Group II	Group III	Group IV	Group V	Group VI	Group VII
	after 1 month	2-4 months	4-6 months	6-8 months	8-10 months	10-12 months	>12 moths
Cylosporine dosage (mg/kg) Mean ± SD	2.2 ± 0.8	2.4 ± 1.6	2.5 ± 1.6	2.6 ± 0.7	2.5 ± 0.7	2.5 ± 0.9	2.2 ± 0.9
Cylosporine trough level (ng/ml) Mean ± SD	188.9 ± 112.9	180.3 ±120.9	180.9 ± 97.7	166.6 ± 82.4	187.7 ± 75.6	176.5 ± 79.1	170.3 ± 91.3
Cylosporine peak level (ng/ml) Mean ± SD	841.1 ± 492.8	819.6 ± 339.8	756.3 ± 367.9	809.4 ± 317.7	867.6 ± 331.8	697.1 ± 290.9	762.4 ± 492.7
Serum creatinine (mg/dl) Mean ± SD	1.3 ± 0.3	1.2 ± 0.8	1.1 ± 0.8	1.5 ± 0.9	1.5 ± 0.8	1.4 ± 1.2	1.4 ± 0.9
Glomerular filtration rate (mL/min) Mean ± SD	94.5 ± 38.9	80.8 ± 37.3	81.1 ± 41.2	87.4 ± 66.9	95.4 ± 88.1	96.8 ± 47.5	96.9 ± 44.8
Blood urea-nitrogen level Mean ± SD	35.26 ± 22.9	48.17 ± 35.7	50.4 ± 35.3	47.5 ± 37.8	52.1 ± 31.9	46.1 ± 34.7	38.6 ± 32.1
Blood urea level Mean ± SD	32.6 ± 27.4	35.1 ± 39.5	46.5 ± 47.6	29.4 ± 35.3	26.6 ± 36.6	22.5 ± 11.2	33.4 ± 4
Serum Glutamic Pyruvic Transaminase (IU/L) Mean ± SD	32.9 ± 15.1	34.7 ± 17.7	35.3 ± 17.5	39.1 ± 20.4	33.1 ± 14.1	33.7 ± 14.6	29.9 ± 13.9
Serum Glutamic Oxaloacetic Transaminase (IU/L) Mean ± SD	20.2 ± 9.1	20.9 ± 15.2	21.1 ± 12.8	24.7 ± 18.7	25.1 ± 17.3	21.9 ± 13.1	21.7 ± 16.8
Serum Albumin Level (mg/dl) AMean ± SD	6.8 ± 3.4	4.4 ± 2.3	3.4 ± 0.6	3.4 ± 0.8	3.3 ± 0.5	3.8 ± 3.2	3.6 ± 0.6

Table 5: Dosage of cyclosporine, levels of trough-peak, hepatic as well as profiles of renal functions in renal transplantation under diversified post-transplant intervals (n=522).

Serum Glutamic Oxaloacetic Transaminase								
r=0.345 p=0.000**	Serum Glutamic Pyruvic Transaminase							
r=0.013 p=0.727	r=0.003 p=0.940	Serum Albumin Level						
r=0.018 p=0.622	r=0.045 p=0.232	r=0.049 p=0.189	Blood Urea Level					
r=0.018 p=0.232	r=0.103 p=0.006**	r=0.049 p=0.804	r=0.12 p=0.000**	Blood Urea & Nitrogen				
r=0.013 p=0.725	r=0.041 p=0.272	r=0.017 p=0.651	r=0.024 p=0.525	r=0.18 p=0.624	Creatinine Clearance			
r=0.006 p=0.908	r=0.097 p=0.009**	r=0.022 p=0.662	r=0.014 p=0.1782	r=0.02 p=0.0592*	r=0.067 p=0.194	Cyclosporine Peak Level		
r=0.089 p=0.000	r=0.052 p=0.169	r=0.063 p=0.045*	r=0.014 p=0.708	r=0.016 p=0.665	r=0.001 p=0.980	r=0.411 p=0.000**	Cyclosporine Trough Level	
r=0.025 p=0.479	r=0.097 p=0.009**	r=0.01 p=0.789	r=0.112 p=0.003**	r=0.109 p=0.003**	r=0.037 p=0.316	r=0.05 p=0.917	r=0.025 p=0.479	Cyclosporine Dosage

**Correlation is significant at the 0.01 level
*Correlation is significant at the 0.05 level

Table 6: Attained correlation with the co-efficient as well as statistical p-values indicator noted among diversified laboratory variables as well as daily dosage of cyclosporine (n=522).

within a of 30%-40% under minimal quantity of oral dose that demand content without determined increase in rejection [14]. Still, there is the impairment meant towards renal functions with frequent adversity in relation with toxic effect led by cyclosporine therapy [15].

Adjustment of dosage during that phase calculated notable empirical aspect as per retrospective analysis made over the data of patient in the span of early years of the transplantation of organ [16]. This research depend over the target to minimize the aspect of immune suppression added by the rejection of toxic hypertensive mode without any sort of adverse condition that affect rejection centered over the reductions of the dosage in relation with immediate, good, and long term consequences [17]. In the present work, the mean cyclosporine dosage was 2.5 ± 1.1 mg/kg. It was marked low than the reference cyclosporine dosage regarding maintenance dose (5-10 mg/Kg). Similarly, Arway et al. [18] found cyclosporine dosage in renal transplant receipt was 2.6 ± 0.9 mg/kg. On the other hand, Russel et al. [19] were needed to give a cyclosporine at a dosage of 12 mg/kg/d at one month followed by 5.5 mg/kg/d as a maintenance dose. After a span of 4 years, basic cyclosporine dose drop to a range of 4.0 mg/kg/day, whereby the studied patients graft the survival rate as 67%. Dosage of high cyclosporine in previous study can offer attribution towards high percentage related to the graft rejection within total mode of hepatic transplantation rather than the process of renal transplantation.

This research follows the mode of observing frequencies in relation with toxic cyclosporine under clinical effects that gets noted through variable mode of cyclosporine concentration added by the detection of efficiency degree marked for the lower therapeutic trough in the cyclosporine concentration (where the trough level remains within 150-200 ng/ml) and get possible under minimal effect of toxin without increased rejection risk. Current dosage of cyclosporine protocol that make adjustment towards lower level of dosage offered for the recipient of the renal transplant at Dammam Medical Complex added by Qatif Central Hospital for the department of renal transplant as per prior declared instances. Current protocol for cyclosporine governs the initial functions of the renal status in relevance to the non-therapeutic monitoring of the drug as the level of serum creatinine,

blood/nitrogen/urea levels, added by hepatic functions tests for the assessment of serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase and level of serum albumin. Followed by a therapeutic monitoring drug by inspection gets noted through the cyclosporine concentration of the trough–peak meant for some postoperative intervals of time, where this aspect offers opportunity towards the analysis of impact led over lower concentration of the normal cyclosporine trough-peak (level from 150-200 ng/ml trough per 700-800 ng/ml peak) within the transplantation operation of the renal related patients.

As per the collected data, patients with renal aspect are inclusive of moments treated added by cyclosporine towards the note of reaching adjusted mean for the levels of trough (that is between 150-200 ng/ml) added by 700-800 ng/ml towards the levels of cyclosporine peak in the time of first postoperative that is within a span of 15 months.

Slight increase has been noted by the current researcher in the mean serum creatinine level 1.3 ± 0.9 mg/L with moderate decrease in the mean creatinine clearance 89.1 ± 50.8 ml/min were observed in the studied renal transplant receipts. As per the prior mentioned level of creatinine added by the clearance results under multiple studies were documented [18,20,21]. Various levels are considered for the clearance of creatinine and aspect of creatinine in terms of accepting ranges that are commented over prior mentioned derivation of creatinine within adequate amount of good ranges noted within first year in terms of patients with post transplant status.

Current research classifies renal transplant recipients into 3 determined categories towards cyclosporine trough as well as levels of peak (therapeutic, sub-therapeutic and ranges of toxin). Various renal receipt get represented under abnormal mode of higher concentration of blood cyclosporine that are poorly adjusted through the toxic cases of cyclosporine, where concentration percentages of toxic cyclosporine that increase up to 11.15% as well as 33.3% within concentration of trough-peak cyclosporine respectively. Researchers note higher percentage caused by poor dosage of adjustments and monitoring meant for cyclosporine medication, as a determined toxin group signs are marked in these cases. In reference to the current research; there are different studies by Brunet et al. [3], as well as Maryam et al. [21], who came up with the validity as well as efficiency related to the meticulous concentration of the cyclosporine monitoring as well as adjusting dosage at lower level towards the avoidance of therapy related to the effects of toxic cyclosporine immune suppression in patients with renal transplant Maryam et al. [21].

The research based variables for toxicokinetic related to the concentration of toxic cyclosporine within recipients of renal transplant reveal important changes in terms of constant elimination, distribution of volume added by the half lives of cyclosporine in comparison with normal and any sorts of cases. All these change of toxicokinetics instances offer negative impact within the pattern of drug kinetics within the recipients of renal transplant caused towards excess mode of concentration related to the level of blood cyclosporine within body compartments. As per former results attained by Alberto et al. [22], as well as Bernard et al. [23], there are similar changes noted in cyclosporine toxicokinetic in reference to the cases of toxic cyclosporine in comparison with the levels of eutherapeutic cyclosporine by concentrating over important prolonged cyclosporine that is within half lives and is noted through volume of distribution expansion.

Results under discrepancy in present research get noted from other modes of studies related to cyclosporine pharmacokinetic or the parameters of toxicokinetic noted towards diversified higher dosage of regimens noted within other sorts of research studies; as for instance, mean dose for cyclosporine attained by the patients of kidney transplant in a transplant centre, China had 4.6 mg/kg noted within two divided modes of doses [24]. A study conducted in Japan by Tokui et al. illustrated the values of the cyclosporine pharmacokinetic parameters in a controlled renal transplant patient to be 0.547 ± 0.033 hr^{-1} for the mean K_e, 147.1 L for the V/F, and 23.7 L/hr for the oral clearance [25].

Moreover, 2 former researches have shown values related to such parameters of cyclosporine toxicokinetic aspect. First study [26] offers CL/F as 28.5 L/hr added by V/F as 133 L that result from 4.1 mg/kg cyclosporine dosage. Next research [27] derived CL/F value as 22.1 L/hr added by V/F as147 L for respective population with Cs dasage 3.5 mg/kg. Lastly, there are toxicokinetic aspects offered values from former studies that were diversified in nature in reference to the current study. According to Tokui et al. [25] AUC gets meant for all sorts of kidney transplanted patients with a mean of 2290 ± 505 ng/ml/hr that remain lower than value attained by current study [25]. This variation are caused by diversified immune suppressant protocols, diversified cyclosporine therapeutic aspects and ranges of toxic entities under different sorts of immunoassays as implied (High Performance Liquid Chromatography, Radio Immuno Assay or Florescent Polarization Immunoassay) within centers of transplantations on international basis. Moreover, there is non-compliance made along with the medication process that remain irregular for visiting purposes in hospital and can offer diversified levels of cyclosporine. Limitation gets noted for this current research with effect over interaction of drug-food in reference to concentration of cyclosporine serum that never gets investigated.

There are recent improvements noted by the current researchers, yet the same remains non-significant in terms of cyclosporine kinetics over normal range of cyclosporine group in comparison with high normal existence, particularly under decreased mode of half life as well as increased rate of cyclosporine clearance, concurrent as per the derived results. As clarified by Benard et al. [23], renal transplant with cyclosporine medication under the therapeutic range between 150 to 200 ng/dl get preserved through the functionalities of renal context as per improvement noted within the parameters of cyclosporine kinetics [Ke, 0.24 ± 0.21 (hr^{-1}), $t_{½}$ 5.1 ± 1.7 (L/hr) added by AUC 9877.1 ± 355 (ng/ml/hr)].

The core concern of the current research depends on the detection related to diversified effects of cyclosporine toxin frequencies in terms of time span of variable transplantation phases. Basic demand for the success of noted therapy through cyclosporine gets imposed by the functions of transplantation managed without the effects of toxin [28]. By means of ephrotoxicity of the therapy under cyclosporine added by level of serum, many monitoring of toxicology drug centers make adjustments over dose meant under the level of serum concentration, which are monitored cautiously [29]. In case of cyclosporine being within referential limits, effects of toxin remain unnoticed. By the application of dose optimization, transplant gets rejected along with toxicity [30].

Current research gets noted through hypertension that remains most frequent for the condition of effects related to cyclosporine toxin. The matter is for 14% of total study made over recipient of renal transplant. Instance of hypertension gets induced through cyclosporine and never in relation with effect of vasoconstrictor aspect, yet in reference to worse sort of endothelium reliance of relaxation managed through Prostacyclin. Decrease of sodium-potassium pumping in cyclosporine can be the result of hypertension [31]. In the same way, current study by

Mensura et al. [32] shows 16% incidence meant for hypertensive mode of inducement over cyclosporine toxic effect through four postoperative years. Moreover, cyclosporine increase by double instance that reports percentage related to a study in relation with research led by Anil et al. [33] there is the noted percentage managed through the application of higher mode of cyclosporine dosage protocol between 7-10 mg/kg/day under two divided doses.

In order to evaluate connection among the status of hypertensive frequencies added by cyclosporine toxic, the approach is noted within the therapeutic ranges. Current research offers prevalent hypertensive status of concentrated toxic cyclosporine tough in reference to high normal range of therapeutic trough (200-300 ng/ml) added by lower mode of normal therapeutic range of cyclosporine therapeutic status (150-200 ng/ml). These are noted through the following numerical instances of 40, 17 and 4 numerical hypertensive status respectively with associated blood samples. Under the current research in Switzerland [34] with an assessment towards the nitroglycerine effect over cyclosporine that gets induced within hypertension noted after the operation of organ transplantation. These aspects clarify notable instances of increased conditions of cyclosporine that gets induced within the hypertension in relation with the dosage of higher cyclosporine in comparison to the lower dosage as well as the noted categories of nitroglycerine offering effective therapeutic effects in a lowered mode of hypertension.

Effects of cyclosporine are hardly directed over the immune system, yet the status of toxin starts with the expansion of variable systems of the body as neurotoxic, gastrointestinal and dermal effects of toxin. Moreover, the core manifestation of toxic cyclosporine beside hypertension can turn tremorous, with visual impairment, instances of gingival hyperplasia and above all hirsutism. Current study reflects the tremor as well as visual impairment by the process of representation made through the effects of toxin after the instance of hypertension within renal recipient; where they represent 10% and 3%, respectively. In accordance to the former two toxicity forms, hirsutism as well as gum hyperplasia remain least possible than 1% of all the reported cases. Various effects of toxin mentioned earlier get noted under higher levels of therapeutic trough cyclosporine, whereas just two cases (tremor and visual impairment) have lower normal range of therapeutic trough. There are some similar sorts of derivations where the research remain under observational study as per the effects of the toxin of cyclosporine treatment within 19 years of adolescent along with kidney transplant in reference to 7 years of observational time span [32]. There are determined numerical sorts of knowledge related to the toxic effects of cyclosporine as tremor, gums' overgrowth and hirsutism; that the tremor remains detected under four cases as well as visual impairment along with hirsutism just for two cases for each.

Researches for this study are well aware of limitations related to current analysis, where the result interpretations must be followed cautiously, as the same is noted within average calculations without reflecting individual liability in reference to the cyclosporine related renal/hepatic toxicities. Moreover, there are some debates if the levels of serum creatinine suffice like a substitution in terms of creatinine clearance meant for renal function evaluation. Moran as well as co-investigators [35] derived creatinine that is poorly cleared in correlation with severity of the toxicated renal function within the renal transplant recipients who gets treated by cyclosporine. Scholars like Myers [36] and Berlyne [37] offer enough correlation among the levels of serum creatinine and rate of glomerular filtration. The results derived in the current research offer similarities noted with Moran et al. without any connection among clearance of creatinine and dosage of cyclosporine. There is no connection that attributes as creatinine as well as analytical parameter of creatinine with poor indicators towards renal function as in case of comparing blood urea and nitrogen level added by urea levels (where p value=0.313).

Still, as the function of renal area get evaluated through similar process thoroughly among all the studied patients added by renal function's impairment degree of assessment in terms of being an indicator towards toxic effect led by cyclosporine that is the core issue of this research, and as such can assume towards the assessment attained through renal function through the serum creatinine, clearance of creatinine, urea in blood and nitrogen added by the level of blood urea that are necessary towards determined parameters. To conclude form statistical implications, the applied research showed that blood urea as well as level of nitrogen is important statistical indicator related to the renal status under cases of transplanted receipt towards dosage of cyclosporine (p value<0.003). According to the research of Khosroshahi et al. [38], low-dose cyclosporine in connection with renal function is within kidney allograph receipts. There is a determined decrease in blood urea level and nitrogen among studied group attained by lower cyclosporine dosage than receipt of high dose, and as such the low-dose noted for cyclosporine at an initial state and the state after transplantation surgery that gets preserved under the function of early allograft without effects of deleterious in graft process.

Cyclosporine's hepatoxicity has been noted as one of frequent undesirable effects of toxic instance. Most frequent approach has been marked by the expression of cyclosporine that is with greater dosages. It is under bio-availability related to cyclosporine that increase in due time in a way that the lower concentration demands for kidney graft [39]. The way to assess hepatic impairment degree in reference to the current research as evaluated under diversified variables marked under hepatic parameters like serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase and level of serum albumin. Slight mode of elevation gets noted through transaminase enzymes added by depression within the level of serum albumin derived through all over immunosuppressive way towards the period of study. Moreover, evidence related to the biochemical instance of hepatic impairment that is given towards important connection between the inverse instance of cyclosporine trough and serum glutamic oxaloacetic transaminase (p value 0.0017), added by the connection between dosage of cyclosporine as well as serum albumin (as in p value 0.0045). Similar derivations are noted for the hepatic impairment under the status of immunosuppressant attained from cyclosporine therapy as noted in various literatures [39,40]. Hepatoxicity remains reversible added by phenomenon relies over dose. The same turns frequent for people with prior instances of defective liver function [40].

Conclusion

In order to conclude, results attained from the current research show in patients who are with renal transplant allograph; added by determined cyclosporine levels of trough are noted as being safely lowered within a range of 150 to 200 ng/ml in terms of minimal mode of toxic effect of cyclosporine added by the instance of being without increased sort of risk for the rejection of graft. In reference to this reduction, there are preservations or modes of improvement attained in the functionalities of renal as well as hepatic actions. Continuous monitoring through laboratory for renal as well as hepatic function tests, particularly for the level of blood urea as well as levels of serum transaminase must get considered instantly with hand on hand note of serum cyclosporine levels of trough-peak caused by determined values of monitoring effects of cyclosporine toxic.

References

1. Ellenhorn MJ (1997) Immunotoxicology–Cyclosporine. Williams and Wilkin, Baltimore.
2. Morris RG (2003) Cyclosporin therapeutic drug monitoring--an established service revisited. Clin Biochem Rev 24: 33-46.
3. Wacke R, Drewelow B, Kundt G, Hehl EM, Bast R, et al. (2001) Cyclosporine A: peak or trough level monitoring in renal transplant recipients? Transplant Proc 33: 3122-3123.
4. Brunet M, Millán O, Jiménez O, Campistol JM, Vidal E, et al. (2004) New concepts in cyclosporine pharmacokinetic and dynamic monitoring: the impact of concomitant immunosuppression on target C2 concentrations. Transplant Proc 36: 437S-441S.
5. Halim MA, Said T, Al-Otaibi T, Eleawa S, Al-Maged H, et al. (2007) Single daily dose administration of cyclosporine in renal transplant recipients. Transplant Proc 39: 1225-1227.
6. Citterio F, Scatà MC, Romagnoli J, Nanni G, Castagneto M (2005) Results of a three-year prospective study of C2 monitoring in long-term renal transplant recipients receiving cyclosporine microemulsion. Transplantation 79: 802-806.
7. Gadela SR, Varma PP, Baliga KV (2004) 3 year prospective evaluation of conversion to C2 monitoring of Renal Transplantation Recipient. Indian J Nephrol 14: 141.
8. Alghamdi S, Nabi Z, Skolnik E, Alkorbi L, Albaqumi M (2011) Cyclosporine versus tacrolimus maintenance therapy in renal transplant. Exp Clin Transplant 9: 170-174.
9. Islam SI, Masuda QN, Bolaji OO, Shaheen FM, Sheikh IA (1996) Possible interaction between cyclosporine and glibenclamide in posttransplant diabetic patients. Ther Drug Monit 18: 624-626.
10. Danovitch, GM (2005) Immunosuppressive medications and protocols for kidney transplantation. In: Danovitch GM (ed.), Handbook of kidney transplantation. Lippincott Williams & Wilkins, Philadelphia, USA.
11. Dressler DK (1992) Monitoring and prevention of renal dysfunction in cardiac transplant recipients. AACN Clin Issues Crit Care Nurs 3: 633-639.
12. Myers BD, Newton L (1991) Cyclosporine-induced chronic nephropathy: an obliterative microvascular renal injury. J Am Soc Nephrol 2: S45-S52.
13. Bieber CP, Reitz BA, Jamieson SW, Oyer PE, Stinson EB (1980) Malignant lymphoma in cyclosporin A treated allograft recipients. Lancet 1: 43.
14. Olivari MT, Kubo SH, Braunlin EA, Bolman RM, Ring WS (1990) Five-year experience with triple-drug immunosuppressive therapy in cardiac transplantation. Circulation 82: IV276-280.
15. Strom TB, Loertscher R (1984) Cyclosporin-induced nephrotoxicity. Inevitable and intractable?. N Engl J Med 311: 728-729.
16. Elliott WJ, Murphy MB, Karp R (1991) Long-term preservation of renal function in hypertensive heart transplant recipients treated with enalapril and a diuretic. J Heart Lung Transplant 10: 373-379.
17. O'Connell JB, Bristow MR, Rasmussen LG, Ratkovec RM, Gay WA Jr, et al. (1990) Cardiac allograft function with corticosteroid-free maintenance immunosuppression. Circulation 82: IV318-321.
18. Arway YA, Noorizan AB, Yahaya H, Muhamed RM, Rozina G (2010) Therapeutic Monitoring Of Cyclosporin In Renal Transplant Patients. Int J Pharm Pharm Sci 2: 224-226.
19. Wiesner RH, Goldstein RM, Donovan JP, Miller CM, Lake JR, et al. (1998) The Impact of Cyclosporine Dose and Level on Acute Rejection and Patient and Graft Survival in Liver Transplant Recipients. Liver Transpl Surg 4: 34-41.
20. Richard N (2002) Long-Term Medical Management for Patient with Kidney Transplants. Hospital Physician Jor. 12: 117-128.
21. Hami M, Mojahedi MJ, Naghibi M, Shakeri MT, Sharifipour F (2010) Cyclosporine Trough Levels and Its Side Effects in Kidney Transplant Recipients. Iran J Kidney Dis 4: 153-157.
22. Magnasco A, Rossi A, Catarsi P, Gusmano R, Ginevri F, et al. (2008) Cyclosporin and Organ Specific Toxicity: Clinical Aspects, Pharmacogenetics and Perspectives. Curr Clin Pharmacol 3: 166-173.
23. Hausen B, Demertzis S, Rohde R, Albes JM, Schäfers HJ, et al. (1994) Low-Dose Cyclosporine Therapy in Triple-Drug Immunosuppression for Heart Transplant Recipients. Ann Thorac Surg 58: 999 -1004.
24. Leung CB, Szeto CC, Ho CS, Law WK, Lam CW, et al. (2005) Pharmacokinetic advantages of two-hour post-dose cyclosporin a level for the therapeutic drug monitoring in stable Chinese kidney transplant recipients. Nephron Clin Pract 99: c68-72.
25. Tokui K, Kimata T, Uchida K, Yuasa H, Hayashi Y, et al. (2004) Dose adjustment strategy for oral microemulsion formulation of cyclosporine: population pharmacokinetics-based analysis in kidney transplant patients. Ther Drug Monit 26: 287-294.
26. Wu KH, Cui YM, Guo JF, Zhou Y, Zhai SD, et al. (2005) Population pharmacokinetics of cyclosporine in clinical renal transplant patients. Drug Metab Dispos 33: 1268-1275.
27. Rosenbaum SE, Baheti G, Trull AK, Akhlaghi F (2005) Population pharmacokinetics of cyclosporine in cardiopulmonary transplant recipients. Ther Drug Monit 27: 116-122.
28. Bizollon CA (1992) Control program of interlaboratory quality for the assay of cyclosporine in biological fluids. Therapie 47: 549-554.
29. Kahan BD, Welsh M, Rutzky LP (1995) Challenges in cyclosporine therapy: the role of therapeutic monitoring by area under the curve monitoring. Ther Drug Monit 17: 621-624.
30. Opelz G (1994) Effect of the maintenance immunosuppressive drug regimen on kidney transplant outcome. Transplantation 58: 443-446.
31. Boero R, Basolo C, Guarena C (1998) Alterd erythrocyte sodium transplant recipients treated with cyclosporine. Nature 23:127-130.
32. Asćerić M, Avdić S, Nukić S, Vrabac-Mujcinagić M (2007) Intensive observation of toxic side effects after several-year of cyclosporin treatment in kidney transplant patient. Bosn J Basic Med Sci 7: 132-135.
33. Anil Kumar MS, Irfan Saeed M, Ranganna K, Malat G, Sustento-Reodica N, et al. (2010) Comparison of four different immunosuppression protocols without long-term steroid therapy in kidney recipients monitored by surveillance biopsy: five-year outcomes. Transpl Immunol 20: 32-42.
34. Sudano I, Farshad M, Flammer AJ, Spieker L, Periat D, et al. (2010) Acute effect of nitroglycerin on cyclosporine-induced hypertension after cardiac transplantation. Swiss Med Wkly140: 139-145.
35. Moran M, Tomlanovich S, Myers BD (1985) Cyclosporine-induced chronic nephropathy in human recipients of cardiac allografts. Transplant Proc 17: 185-190.
36. Myers BD (1989) What is cyclosporine nephrotoxicity? Transplant Proc 21: 1430-1432.
37. Berlyne GM (1965) Endogenous creatinine clearance and the glomerular filtration rate. Am Heart J 70: 143-145.
38. Khosroshahi HT, Badrogli N, Jahannavard N, Oskuii R, Bahluli A, et al. (2009) Safety of low-dose cyclosporine therapy before transplantation in kidney allograft recipients. Transplant Proc 41: 2757-2760.
39. Kassianides C, Nussenblatt R, Palestine AG, Mellow SD, Hoofnagle JH (1990) Liver injury from cyclosporine A. Dig Dis Sci 35: 693-697.
40. Chicharro Mf, Guarner L, Vilaseca J, Planas M, Malagelada J (2000) Does cyclosporin A worsen liver function in patients with inflammatory bowel disease and total parenteral nutrition? Rev Esp Enferm Dig 92: 68-77.