Cyclosporine Trough Levels and Its Side Effects in Kidney Transplant Recipients

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Introduction. Cyclosporine is the backbone of immunosuppression in kidney transplantation. However, it is associated with side effects, some of which are dose-dependent. We evaluated association between cyclosporine trough level and its side effects.
Materials and Methods. In 50 kidney transplant recipients, serum cyclosporine level, fasting blood glucose, and serum creatinine were measured 7 times during first 6 months after transplantation. The participants were also assessed for blood pressure, hand tremor, and headache at each visit. The relationship between cyclosporine trough level and hypertension, hyperglycemia, hand tremor, and headache were evaluated.
Results. There were no significant relationship between cyclosporine levels and allograft function. Except at the second week and sixth month, there were no significant differences between drug doses in various serum cyclosporine trough level groups. At the second week, the mean drug dose in patients with cyclosporine trough levels less than the target therapeutic level was 279.16 ± 56.23 mg/d, while in the patients with cyclosporine levels higher than the therapeutic level, its dose was 302.08 ± 66.61 mg/d ($P < .05$). At the sixth month, the mean drug dose was 137.50 ± 17.67 mg/d in the patients with lower than target cyclosporine levels, and it was 242.18 ± 58.25 mg/d in those with cyclosporine levels higher than the therapeutic level ($P < .05$). There was no significant relationship between serum cyclosporine level and its side effects.
Conclusions. We demonstrated cyclosporine trough level had no direct relation with drug side effects and it is not a suitable measure for assessment of drug side effects.

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INTRODUCTION

It is suggested that cyclosporine blood level in kidney transplant recipients be regulated intensively,[1] as this drug has a narrow and limited therapeutic level.[2] There are different methods of assessing drug level, the oldest of which is measurement of the trough (C0) level that is commonly used even to date.[3-7] Other newer methods consist of the measurement of the area under the curve and the peak level.[8] However, the C0 level monitoring is still wildly used, in spite of its poor relationship with the area under the curve.[9]

Despite maintaining the C0 level within therapeutic levels, a significant group of patients experience either a acute rejection episode or nephrotoxicity.[10] Also, it has been reported that regulation of drug dosage with C0 level monitoring in maintenance of kidney transplant recipients

predispose them to elevated blood pressure and higher blood glucose.[1] On the other hand, some of the side effects of cyclosporine like hyperglycemia, tremor, and headache are related to the drug dosage, while some of them like hypertension are not.[11]

Cyclosporine trough level monitoring is used as a routine method in our center. Therefore, we studied the relation between cyclosporine C0 level and its effects in our patients in the first 6 months after transplantation.

MATERIALS AND METHODS

Patients

All of the kidney allograft recipients in Ghaem Hospital and Imam Reza Hospital who had a kidney transplant from March to November 2006 were enrolled in the study. They received their allografts from either living or cadaveric donors. We excluded patients with severe heart failure, severe hepatic failure, severe hypertension, drug protocols that included polycolonal or monocolonal antibodies, drugs that have effects on cyclosporine level, urologic problems, an age less than 18 years old, and a history of acute rejection in the 1st week after transplantation.

Immunosuppression

Treatment protocol in all of the kidney allograft recipients was a combination of cyclosporine (Neoral, Novartis, Basel, Switzerland), mycophenolate mofetil (Cellcept, Roche, Basel, Switzerland), and prednisolone. All of the patients received cyclosporine, 9 mg/kg to 10 mg/kg, in the 1st posttransplant day, and then, 4 mg/kg to 5mg/kg per day, divided in a twice daily dosage, adjusted based on the C0 level. Mycophenolate mofetil was administered in a fixed dose during the study period, 1 g, twice daily. However, its dose was adjusted to maintain a leukocyte count higher than 3500×10^9/L and a platelet count higher than 80×10^9/L. Methylprednisolone succinate, 500 mg/d to 750 mg/d, was administered intravenously in 1st 3 days, based on the patient's weight (750 mg/d for those with a weight greater than 60 kg and 500 mg/d for those weighed 60 kg or less). Thereafter, prednisolone, 1 mg/kg/d was administered orally and tapered over 3 months to 10 mg/d to 15 mg/d that continued up to 6 months.

Follow-up

Serum C0 level was measured 7 times, on the 4th day, 1st and 2nd weeks, and 1st, 2nd, 4th, and 6th month, during the first 6 months after transplantation. Measurement of cyclosporine was done by direct monoclonal radioimmunoassay in a whole blood sample drawn 12 hours after the night dose of cyclosporine (just before the next dosage). Dose adjustments were made according to the measured C0 level (250 ng/mL to 350 ng/mL in 1st 2 months and 100 ng/mL to 250 ng/mL from months 2 to 6 after transplantation). Also, serum level of creatinine, glomerular filtration rate (estimated by the modification of diet in renal disease formula), fasting blood glucose were recorded. Physical signs and symptoms such as high blood pressure, tremor, and headache were assessed. The study end point was defined as discontinuation of the study protocol due to severe infection or delayed graft function that need more than one sessions of hemodialysis after transplantation.

Statistical Analyses

Continuous variables were expressed as mean ± standard deviation. The independent *t* test and the 1-way analysis of variance test were used for comparison of continuous variables among groups after checking the normal distribution of data. The chi-square test was used for assessment of relationships between qualitative variables. In addition, we studied variations among each variable in 7 levels by the general linear modeling repeated measures. Statistical significance was assumed at a *P* value less than .05.

RESULTS

Of 106 patients that received an allograft from March to November 2006 at our center, 70 met the inclusion criteria and entered study. However, 20 patients were excluded during the study, due to urologic problems, life-threatening infections that led to change in drug protocol, and irregular admissions in clinics. Thus, 50 patients completed the study and were included in the analyses. The mean age of these patients was 34.84 ± 12.37 years old. They were 26 men (52%) and 24 women (48%). Cadaveric donor was the source in 13 transplants (26%) and living unrelated donor in 37 (74%). All except 1 patient received their first kidney transplant.

The laboratory and clinical data of the participants are summarized in Table 1, respectively. There

Table 1. Laboratory and Clinical Characteristics of Kidney Allograft Recipients

Parameter	Posttransplant Period						
	Day 4	Week 1	Week 2	Month 1	Month 2	Month 4	Month 6
Cyclosporine trough level, ng/mL	248.86 ± 102.01	218.03 ± 83.60	237.56 ± 100.86	270.96 ± 86.67	291.30 ± 110.13	233.66 ± 77.90	215.50 ± 69.49
Cyclosporine dose, mg/d	430.22 ± 424.68	399.77 ± 428.03	304.16 ± 64.06	280.72 ± 57.94	259.89 ± 47.47	232.29 ± 46.97	218.75 ± 48.51
Fasting blood glucose, mg/dL	143.50 ± 59.22	134.39 ± 58.09	117.53 ± 46.53	99.28 ± 38.08	109.75 ± 66.10	99.60 ± 29.15	94.82 ± 34.96
Serum creatinine, mg/dL	1.77 ± 0.72	1.58 ± 0.59	1.50 ± 0.42	1.32 ± 0.33	1.35 ± 0.39	1.29 ± 0.33	1.31 ± 0.36
Glomerular filtration rate, mL/min	48.75 ± 20.55	54.01 ± 20.77	54.99 ± 19.09	61.74 ± 18.81	62.97 ± 24.88	64.71 ± 21.81	64.59 ± 23.76
Systolic blood pressure, cm Hg	14.22 ± 1.53	14.01 ± 1.65	13.64 ± 1.55	13.56 ± 1.82	13.25 ± 1.81	13.30 ± 1.66	13.39 ± 1.89
Diastolic blood pressure, cm Hg	8.63 ± 1.20	8.54 ± 1.02	8.47 ± 1.02	7.84 ± 1.18	7.55 ± 1.32	7.73 ± 1.20	7.85 ± 1.27

were no significant relationships neither between serum cyclosporine levels and graft function in any of the assessments, nor between cyclosporine dose and C0 level of cyclosporine, except at the 2nd week and 6th month after transplantation; on the 2nd week, the patients with a C0 level less than therapeutic level took lower doses of the drug than the patients with levels within the therapeutic level and higher than that (279.16 ± 56.23 mg/d versus 296.42 ± 65.16 mg/d and 242.18 ± 58.25 mg/d, respectively; $P < .05$). On month 6, the patients with C0 levels less than the therapeutic level took lower drug loses than those with C0 levels within the therapeutic level or higher than that (137.50 ± 17.67 mg/d versus 209.82 ± 34.92 mg/d and 242.18 ± 58.25 mg/d, respectively; $P < .05$).

At the 4th month after transplantation, the patients with C0 levels less than the therapeutic level had a mean fasting blood glucose higher (183.00 ± 27.03 mg/dL) than patients with C0 levels within the therapeutic level (89.56 ± 16.97 mg/dL) and higher than that (100.84 ± 30.48 mg/dL; $P < .05$).

The frequencies of tremor and headache during the study period are depicted in Table 2. From the 4th day to the 1st month after transplantation, none of the patients with C0 levels higher than the therapeutic level had tremor, while 12.4% of the patients with a C0 level within the therapeutic level and 14.4% with C0 levels lower than the therapeutic level had tremor. After the 4th month, none of the patients with low C0 levels had tremor, but 24.7% of the patients with C0 levels within the therapeutic level and 66.7% with C0 levels higher than the therapeutic level had tremor. We did not find any significant relation between headache and C0 level, as none of the patients with C0 levels higher than normal had headache.

Significant differences were seen between the measured mean values of C0 level, cyclosporine dose, blood glucose, serum creatinine, glomerular filtration rate, and systolic and diastolic blood pressure during the study period in each group; the

Table 2. Frequency of Tremor and Headache in Kidney Allograft Recipients Receiving Cyclosporine*

Parameter	Posttransplant Period						
	Day 4	Week 1	Week 2	Month 1	Month 2	Month 4	Month 6
Tremor	3 (6)	6 (12)	10 (20)	12 (24)	15 (30)	18 (36)	8 (16)
Headache	1 (2)	0	0	4 (8)	1 (2)	0	0

*Values in parentheses are percents.

mean C0 level, cyclosporine dose, serum creatinine, blood glucose, and blood pressure decreased in each assessment, and the mean glomerular filtration rate increased gradually during the study (Table 1).

DISCUSSION

Intrapatients variability in C0 level of cyclosporine is to be more than 36%. This variation can be associated a higher risk of chronic rejection. This condition is more common at the first months after transplantation.[12] Therefore, regulation of drug dosage only based on C0 level, especially in the first months after transplantation, may be associated with a higher risk of graft dysfunction. On the other hand, in some studies, it has been reported that there is a weak relation between C0 level and drug efficacy.[13] In a series, none of patients with C0 levels less than the therapeutic level experienced graft rejection, but 30% of the subjects with C0 levels within the therapeutic range had acute rejection.[14] We did not find a significant relation between C0 level and graft function or acute rejection episodes.

In many studies, it has been reported that cyclosporine monitoring by assessing C0 levels is associated with higher risks of hypertension, hyperlipidemia, and diabetes mellitus.[15,16] One study reported that the incidence of hypertension, hyperlipidemia, and posttransplant diabetes mellitus was similar between two groups which were monitored by C0 and C2 levels.[15] Rodrigo and colleagues found that there were no significant differences between the capacities of C2 and C0 to predict cyclosporine side effects and that both of them are useful.[17] Another study reported that a single daily dose of cyclosporine had the advantage of decreasing dosage and its side effects, while adjusted based on C0 level.[18] Based on our study, there was no significant relation between C0 level and blood glucose or blood pressure. Even at the 4th month after transplantation, the patients with high C0 levels had lower blood glucose levels.

A study in Norway showed that kidney transplant recipients with higher C2 levels were more likely to develop cyclosporine toxicity, while 39% of them had low to normal C0 levels.[16] We did not find any significant relation between C0 level and cyclosporine toxicity. Although during the first 3 months after transplantation, all of the patients with hand tremor had C0 levels within the therapeutic range or lower than it, after that period, the condition was changed; most of the patients with hand tremor were in the group with a high C0 level. We found, in spite of gradual reduction in cyclosporine dose during the study period, C0 levels were changed intermittently into lower and higher levels. Thus, we can suppose drug dose does not have a direct relation with the drug trough level.

CONCLUSIONS

We demonstrated that in kidney transplant recipients receiving cyclosporine, C0 monitoring during the first months after transplantation was not a suitable method for assessment of drug side effects. It has been suggested that drug side effects are more related with the area under the curve of cyclosporine level.[11] Therefore, our results confirmed the previous reports that C0 level correlated poorly with the area under the curve, especially in the first months after transplantation.

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CONFLICT OF INTEREST

None declared.

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