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A Study on Clinical, Biochemical, Drug Trough Level and Histopathological Correlation of Calcineurin Inhibitor (CNI) Toxicity in Renal Allograft Recipients

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Abstract:- Calcineurin inhibitor revolutionized the renal allograft transplant outcome. However it causes nephrotoxicity in long run. The serum trough level of the drug does not correlate with degree of nephrotoxicity because of its varied pharmocokinetics, narrow therapeutic index, and individual sensitivity to toxic levels. Toxicity clinically characterised by tremor, hypertension, hyperuricemia, histopathologically by isometric vacuolization, arterial nodular hyalinosis, striped fibrosis and interstitial atrophy. This study conducted at Rajiv Gandhi Government General hospital, Chennai from June 2012 to June2013. Sixty one patients were included in this study. Clinical toxic features, drug trough level, biochemical parameters were recorded in 0-3, 3-6, 6-9, more than 9 months were recorded. Allograft biopsy and histopathology examinations were done when required with patient consent. Prevalence of clinical calcineurin inhibitor toxicity was 60.7 %(37), 39.3% (24), 25.4% (15) and 23.3%(10) at 0-3, 3-6, 6-9, and >9 months respectively. Among clinical features tremor and hypertension were present in majority of the recipients [tremor: 39.3% (24), 34.4% (21) , 25.4% (15) and 20.9% (9); hypertension: 39.3% (24), 31.1% (19), 13.6% (6) and 7% (3) at 0-3, 3-6, 6-9 and >9 months respectively]. NODAT was present in 4.9% (93) in 0-3 & 3-6 months, 6.8% (4) in 6-9 months and 2.3% (1) in more than 9 months. Graft dysfunction was in 37.7% (23), 23% (14) , 37.3% (22), and 7% (3) at 0-3, 3-6, 6-9 month and thereafter. Elevated trough level was seen in 29.5% (18), 27.9% (17), 32.2% (19) and 18.6% (8) at 0-3, 3-6, 6-9 month and thereafter. In our study a significant correlation between tremor, clinical toxicity and elevated trough (Co) level at 3-6 and 6-9 month (P<0.001) was observed. There was no significant correlation between clinical toxicity, trough level, graft dysfunction and histopathological correlation at 0-3, 36, 6-9 and >9 months. There was a significant correlation between tremor and elevated trough level of calcineurin inhibitor was observed at 3-6 and 6-9 months.

I. INTRODUCTION

Introduction of calcineurin inhibitor in later part of twentieth century revolutionized the history of renal transplantation by reducing the short term morbidity and mortality. However the patients receiving calcineurin inhibitor were under the risk of calcineurin inhibitor nephrotoxicity in long run. The chronic nephrotoxic effects of calcineurin inhibitors associated with the renal parenchymal damage plays a major role in the pathogenesis of chronic renal dysfunction. Calcineurin inhibitor toxicity clinically characterized by tremor, hypertension, hypertrichosis and gum hypertrophy, biochemically by raising creatinine (graft dysfunction), hyperglycemia, hyperkalemia and hyperuricemia and histopathologicaly by isometric vacuolization, arterial nodular hyalinosis, striped fibrosis and interstitial atrophy.

The effect of toxicity was reversible in short term, became irreversible in long term. Lower dose results in graft dysfunction and rejection, higher dose results in toxicity because of its narrow therapeutic index (little difference between toxic and therapeutic doses). So it was mandatory to adjust its dosage according to measurements of the actual blood levels through therapeutic drug monitoring (TDM). The serum level of drug does not correlat with the degree of nephrotoxicity in most of the occasion because of its varied pharmacokinetics, narrow therapeutic index, individual sensitivity to toxic effects.

II. AIM OF THE STUDY

To study the clinical, biochemical, whole blood trough level and histopathological correlation of calcineurin inhibitors (CNI) toxicity in renal allograft recipients

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III. MATERIALS AND METHODS

A. Study Design

Prospective study.

➢ *Inclusion Criteria*

All end stage renal disease patient who underwent renal transplantation between June 2012 and June 2013 in the department of nephrology, Rajiv Gandhi government general hospital were included.

➢ *Exclusion criteria*

Patients who had Graft dysfunction due to surgical issues, who underwent graft nephrectomy, who expired were excluded. Eligible patients were enrolled. Their demographic profile such as age, sex, type of native kidney disease, type of donor whether live related or deceased, age and sex of donor, type of relation in case live related were collected. In immediate post-operative period if the patient have raising creatinine, complete blood count, peripheral smear study, platelet count, serum lactic dehydrogenase, urine analysis, serum electrolytes, liver function test, urine and blood culture sensitivity were done. USG KUB, Renal Doppler and necessary investigations were done in order to rule out surgery related complication. Whole blood cyclosporine/tacrolimus trough(CO) level was assayed twelve hour after previous dose If the renal dysfunction does not due to surgical complication and patient showed clinical feature of Calcineurin toxicity such as tremor, paresthesia, hypertension(worsening hypertension in need of more drugs and new onset hypertension), paresthesia, gum hypertrophy, hypertrichosis, sodium, potassium, cholesterol were done.

In this study cyclosporine trough level was assayed by enzyme linked microparticle immune assay (EMIA) and tacrolimus trough level was assayed by chemiluscent enzyme linked immune assay(CLEIA). As per our department protocol for those receive induction treatment cyclosporine level was considered in therapeutic range if it was 200-250ng/ml at 0-1month, 100-200 ng/ml at 2-6 months, and around 100 ng/ml after 6months. For tacrolimus, the level was considered in therapeutic range if it was around 8 ng/ml at 0-1 month, 5-6 ng/ml at 36months, 3-5 ng/ml after 6months. For those didn't receive induction, cyclosporine level was considered in therapeutic range if it was 200250ng/ml at 0-1month, 150-200ng/ml at 2-6 months, and around 100-150 ng/ml after 6months. For tacrolimus, the level was considered in therapeutic range if it was around 8-10ng/ml at 0-1 month, 7-8ng/ml at 3-6months, around 5ng/ml after 6months

IV. RESULTS

This study was conducted in our department among End Stage Renal Disease patients who underwent Renal Transplantation from June 2012 to June 2013. A total of sixty one patients were included out of seventy five. Of which males were 83.6% (51) and females were 16.4% (10), (Table 1).

Sex	No	%
Male	51	83.6
Female	10	16.4

Table 1:- Recipient sex

Among Recipients majority of them were in 3rd decade 39.3% (24), followed by equal proportion in 4th 24.6% (15) and 5th decade 24.6% (15), (Table 2). Mean age was 31.45 (range: 17-56years).

Age group	No	%
10-19	3	4.9
20-29	24	39.3
30-39	15	24.6
40-49	15	24.6
50-59	4	6.6

Table 2:- Recipient age group in years

70.5% patients were live related donor recipients and 29.5% were deceased donor recipients. (Table 3).

Type of donor	No	%
Live donor	43	70.5
Deceased donor	18	29.5

Table 3:- Type of Donor

Among live related donor males were 16.7% (7) and females were 83.3% (36) (Table 4).

Sex	No	%
Male	7	16.7
Female	36	83.3

Table 4:- Sex Ratio of Live Donor

Of which mothers were 44.2% (19), followed by spouse 0.2% (13), fathers 16.3% (7) and sisters 9.3% (4), (Table 5).

Relation	No	%
Father	7	16.3
Mother	19	44.2
Spouse	13	30.2
Sister	4	9.3

Table 5:- Relationship among Live donor

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Among deceased donor males were 19.4% (17) and females were 5.6% (1), (Table 6).

Sex	No	%
Male	17	19.4
Female	1	5.6

Table 6:- Deceased donor sex

After renal transplantation recipients were treated with immunosuppressive agents [three drugs: calcineurine Inhibitors (cyclosporine / Tacrolinus) + mycophenolate Mofetile / Azathioprine + Steroids] as per our department protocol. Induction treatment was given as per our department protocol [rabbit Anti Thymocyte Globulin / Interleukin – 2 receptor Antagonist) for high risk recipients such as those received organ from deceased donor, spouse donor and second transplant). These patients were followed up for 0-18 months (mean 12.5 months) for calcineurin inhibitor toxicity. Observed toxic features were grouped into 0-3, 3-6, 6-9 and more than 9 months of post transplant age.

Follow up revealed that toxicity of calcineurin inhibitors were clinically present in 60.7% (37) in 0-3, 39.3% (24) in 3-6, 25.4% (15) in 6-9 months and 23.3% (10) in more than 9 months (Table 7).

Clinical toxicity	0-3 months		3-6 months		6-9months		>9months	
	n	%	n	%	n	%	n	%
Yes	37	60.7	24	39.3	15	25.4	10	23.3
No	24	39.3	37	60.7	44	74.6	33	76.7

Table 7:- Clinical CNI toxicity

Among them, further toxicity profile was evaluated and grouped into 0-3, 3-6, 6-9 and >9 months. Evaluated toxicity profile were tremor, paresthesia, hypertension (new onset /worsening), hypertrichosis, gum hypertrophy and NODAT (based on ADA guidelines) (Table 8).

		0-3 months		3-6 months		6-9months		>9months	
		n	%	n	%	n	%	n	%
Tremor	Yes	24	39.3	21	34.4	15	25.4	9	20.9
	No	37	60.7	40	65.6	44	74.6	34	79.1
Paresthesia	Yes	2	3.3	1	1.6	0	0	0	0
	No	59	96.7	60	98.4	59	100	43	100
Hypertension	Yes	24	39.3	19	31.1	8	13.6	3	7
	No	37	60.7	42	68.9	51	86.4	40	93
Hypertrichosis	Yes	0	0	0	0	1	1.7	3	6.9
	No	61	100	61	100	60	98.3	40	93.1
Gumhypertrophy	Yes	0	0	0	0	1	1.7	1	2.3
	No	61	100	61	100	60	98.3	40	97.7
NODAT	Yes	3	4.9	3	4.9	4	6.8	1	2.3
	No	58	95.1	58	95.1	55	93.2	42	97.7

Table 8:- CNI Toxicity Profile

Tremor was present in 39.3% (24) in 0-3 months, 34.4% (21) in 3-6 months, 25.4% (15) in 6-9 months and 20.9% (9) in more than 9 months. Hypertension was present in 39.3% (24) in 0-3 months, 31.1% (19) in 3-6 months, 13.6% (6) in 6-9 months and 7% (3) in more than 9 months. Hypertrichosis and gum hypertrophy were present in few patients after 6 months of transplant. NODAT was present in 4.9% (93) in 0-3 months and 3-6 months, 6.8% (4) in 6-9 months and 2.3% (1) in more than 9 months.

During follow up improvement in graft dysfunction following tapering with calcineurin inhibitor was presumed to be due to calcineurin inhibitor toxicity after excluding rejection. Table 9 showed that graft dysfunction due to calcineurin inhibitor toxicity.

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	0-3 months		3-6 months		6-9 months		>9 months	
	n	%	N	%	n	%	n	%
Yes	23	37.7	14	23	22	37.3	3	7
No	38	62.3	47	77	37	62.7	40	93

Table 9:- Graft dysfunction

Graft dysfunction was in 37.7% (23) in 0-3 months, 23% (14) in 36 months, 37.3% (22) in 6-9 months, and 7% (3) in more than 9 months. Whole blood trough(Co) level was done. Which shown in

	0-3 months		3-6 months		6-9 months		>9 months	
	n	%	n	%	n	%	n	%
Elevated CO	18	29.5	17	27.9	19	32.2	8	18.6
Normal Co	43	17.5	44	72.1	40	67.8	35	81.4

Table 10:- Trough (Co) level

Elevated trough level was seen in 29.5% (18) in 0-3 months, 27.9% (17) in 3-6 months, 32.2% (19) in 6-9 months and 18.6% (8) in more than 9 months. Biopsy and histopathological examination was done only in small number of patients because of its invasiveness and procedure related complication, patient willingness and improvement with tapering of drugs. Biopsy features were shown in Table 11.

	0-3 months		3-6 months		6-9 months		>9 months	
	No	%	No	%	No	%	No	%
Iso.vacuolization	6	9.8	5	8	2	3.4	0	0
Med. Hyalinosis	2	3.3	1	1.6	0	0	0	0
TMA	1	0	0	0	0	0	0	0
Glomerulosclerosis	0	0	0	0	0	0	0	0
Intertial fibrosis	0	0	1	0	0	0	0	0
Tubular atrophy	0	0	1	0	0	0	0	0
CNI Toxicity	6	9.8	5	8.2	2	3.4	0	0

Table 11:- Histopathological features of CNI toxicity

In 0-3 months Six patients were found to have histopathological features of CNI toxicity. Isometric vacuolization was found in all biopsies, medullary hyalinosis and thrombotic microangiopathy were seen in two and one of those biopsies. In 3-6 months 5 patients shown histopathological evidence of CNI toxicity of which isometric vacuolization was present in all five biopsies and medullary hylinosis present in one biopsy. In 6-9 months, 2 patients were shown evidence of histopathological toxicity, isometric vacuolization was present in both of them.

V. ANALYSIS

Statistical analyses were done by SPSS 20.6 software. Analysis was done in each post transplant age group. Factors analyzed were trough (Co) level (elevated trough (Co) level / normal trough (Co) level) versus clinical toxicity, tremor, paresthesia, hypertension, NODAT, graft dysfunction and histopathological toxicity. Hypertrichosis and gum hypertrophy were not analyzed because of its lower frequency in this study groups.

		Elevated Co	Normal Co	P
Clinical toxicity	Present	14	23	0.077
	Absent	4	20	

Table 12:- Analysis at 0-3 Months -Clinical Toxicity vs Trough Level (0-3 months)

Analysis revealed that no significant correlation between the clinical toxicity and trough (Co) level. Clinical features versus Trough (Co) level (0-3 months).

		Elevated Co	Normal Co	P
Tremor	Present	10	14	0.094
	Absent	8	29	
Paresthesia	Present	1	1	0.518
	Absent	17	42	
Hypertension	Present	6	18	0.534
	Absent	12	25	
NODAT	Present	2	1	0.148
	Absent	16	42	

Table 13

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There is no significant correlation between tremor, paresthesia, hypertension, NODAT and trough (Co) level.

		Elevated Co	**Normal Co**	**P**
Graft dysfunction	**Present**	7	16	0.902
	Absent	11	27	

Table 14:- Graft Dysfunction Vs Trough (Co) level (0-3 months)

Analysis revealed that no significant correlation between the graft dysfunction and trough (Co) level.

		Elevated Co	**Normal Co**	**P**
Histopathological toxicity	Present	1	5	0.468
	Absent	17	38	

Table 15:- Histopathological Toxicity Vs Trough (Co) level (0-3 months)

Analysis revealed that no significant correlation between the histopathological toxicity and trough (Co) level.

		Elevated Co	**Normal Co**	**P**
Clinical toxicity	Present	13	11	0.001
	Absent	4	33	

Table 16:- Analysis at 3-6 Months: Clinical toxicity vs Trough (Co) level (3-6 months)

Analysis revealed that there was significant correlation between the clinical toxicity and trough (Co) level.

		Elevated Co	**Normal Co**	**P**
Tremor	Present	13	8	0.001
	Absent	4	36	
Paresthesia	Present	0	1	0.531
	Absent	17	43	
Hypertension	Present	7	12	0.295
	Absent	10	32	
NODAT	Present	1	2	0.829
	Absent	16	42	

Table 17:- Clinical features Vs Trough (Co) level (3-6 months)

Analysis revealed that there was significant correlation between tremor and elevated trough level. No significant correlation between paresthesia, hypertension, NODAT and elevated trough(Co) level.

		Elevated Co	**Normal Co**	**P**
Graft dysfunction	Present	4	10	0.947
	Absent	13	34	

Table 18:- Graft Dysfunction Vs Trough (Co) level (3-6 months)

Analysis revealed that no significant correlation between the graft dysfunction and trough (Co) level.

		Elevated Co	**Normal Co**	**P**
Histopathological toxicity	Present	0	5	0.147
	Absent	17	39	

Table 19:- Histopathological Toxicity Vs Trough (Co) level (3-6 months)

Analysis revealed that no significant correlation between the histopathological toxicity and trough (Co) level.

		Elevated Co	**Normal Co**	**P**
Clinical toxicity	Present	11	4	0.001
	Absent	8	36	

Table 20:- Analysis at 6-9 Months: Clinical Toxicity Vs Trough (Co) level (6-9 months)

Analysis revealed that there was significant correlation between the clinical toxicity and trough (Co) level.

		Elevated Co	**Normal Co**	**P**
Tremor	Present	12	3	0.001
	Absent	7	37	
Paresthesia	Present	0	0	
	Absent	0	0	
Hypertension	Present	6	2	0.005
	Absent	13	38	
NODAT	Present	2	2	0.430
	Absent	17	38	

Table 21:- Clinical Features Vs Trough (Co) level (6-9 months)

There was significant correlation between tremor and trough level. No significant correlation between paresthesia, hypertension, NODAT and trough level.

		Elevated Co	**Normal Co**	**P**
Graft dysfunction	Present	11	11	0.024
	Absent	8	29	

Table 22:- Graft dysfunction Vs Trough (Co) level (6-9 months)

Analysis revealed that no significant correlation between the Graft dysfunction and trough (Co) level.

		Elevated Co	**Normal Co**	**P**
HPE	Present	2	0	0.37
	Absent	17	40	

Table 23:- Histopathological toxicity Vs Trough level (6-9 months)

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Analysis revealed that no significant correlation between the histopathological toxicity and trough (Co) level.

		Elevated Co	Normal Co	P
Clinical toxicity	Present	7	3	22.72
	Absent	1	32	

Table 24:- Analysis at >9 Months : Clinical Toxicity Vs Trough (Co) level (>9 months)

Analysis revealed that no significant correlation between the Clinical toxicity and trough (Co) level.

		Elevated CO	Normal CO	P
Tremor	Present	6	3	17.36
	Absent	2	32	
Paresthesia	Present	0	0	0
	Absent	0	0	
Hypertension	Present	2	1	4.91
	Absent	6	34	
NODAT	Present	1	0	4.47
	Absent	7	35	

Table 25:- Clinical Features Vs Trough (Co) level (>9 months)

There was no significant correlation between tremor, paresthesia, hypertension, NODAT and trough level.

		Elevated Co	Normal Co	P
Graft dysfunction	Present	1	2	0.462
	Absent	7	33	

Table 26:- Graft Dysfunction Vs Trough (Co) level (>9 months)

Analysis revealed that no significant correlation between the Graft dysfunction and trough (Co) level.

	Clinical toxicity	Elevated Co	GDF	Histopathological Toxicity	P
0-3 months	37	18	23	6	3.28
3-6 months	24	17	14	5	3.81
6-9 months	15	19	22	2	2.86
>9 months	23	8	3	0	1.66

Table 27:-The Correlation between clinical, trough (Co) level, graft function and histopathological toxicity

There was no significant correlation between clinical toxicity, elevated trough level, graft dysfunction, histopathological toxicity at 3-6, 6-9 and > 9 months.

VI. DISCUSSION

In our study total of sixty one renal allograft recipients who underwent renal allograft transplantation from June 2012 to June 2013 at our centre were included. Followed up for the period of 0-18 month (median of 12.5 months) for calcineurin inhibitor toxicity. Out of sixty one 83.6% (51) were male and 16.4 % (10) were female, majority of them were in third decade of life. Among donors, live versus deceased donor was 70.5% (43) and 29.5% (18). Majority of the live donors were mother 44.2 % (19) followed by spouse 30.2% (13).

Prevalence of clinical calcineurin inhibitor toxicity was 60.7%(37), 39.3%(24), 25.4%(15) and 23.3%(10) at 0-3, 3-6, 6-9, and >9 months respect tively. Among clinical features tremor and hypertension were present in majority of the recipients [tremor: 39.3%(24), 34.4% (21) , 25.4% (15) and 20.9% (9); hypertension: 39.3% (24), 31.1% (19), 13.6% (6) and 7% (3) at 0-3, 3-6, 6-9 and >9 months respectively]. NODAT was present in 4.9% (93) in 0-3 & 3-6 months, 6.8% (4) in 6-9 months and 2.3% (1) in more than 9 months. Graft dysfunction was in 37.7% (23), 23% (14) , 37.3% (22), and 7% (3) at 0-3, 3-6, 6-9 month and thereafter. Elevated trough level was seen in 29.5% (18) , 27.9% (17), 32.2% (19) and 18.6% (8) at 0-3, 3-6, 6-9 month and thereafter. Neeraja kambham20 et al shown that incidence of hypertension was 24% at 3 and 6 months and 18% at 12 months. Jose M morale21 et al shown that prevalence of hypertension was 60-85% in patients on calcineurin inhibitors. More than fifty percent of well functioning graft showed arterial hypertension. Vincenti22 et al shown that prevalence of new onset diabetes after trans plantation was 15%.

Zibiti23 et al shown that after a mean transplantation time of three months, 14/92 (15.2%) transplanted patients developed NODAT in his study of 92patients.

Sitagourishankar24 et al shown that prevalence of new onset diabetes was 6.7% at 6 months, 7.0% at 12 months and 8.0% at 3 years post transplant (study on 386 adult kidney transplant recipient). Incidence of new onset diabetes in our study coincides with him.

In our study trough level was significantly correlated with tremor and clinical toxicity at 3-6 and 6-9 month($P<0.001$). Trough level doesn't correlate with tremor, hypertension, NODAT, graft dysfunction. In 0-3 and more than nine months trough level didn't correlate with clinical toxicity, graft dysfunction and histopathological toxicity.

Maryam hami et al shown that in his study among 50 kidney transplant recipients from one week to six months of post transplant age shown that no significant relationships neither between serum cyclosporine levels and graft function nor between cyclosporine dose and CO, except at second week and sixth month after transplantation. After fourth month, none the patients with low Co levels had tremor, but 24.7% of the patients with Co levels within therapeutic level and 66.7% with Co levels higher than the therapeutic level had tremor, no significant relation between Co level and blood glucose and blood pressure.

In our study 6, 5 and 2 patients at 0-3months, 3-6 months and 6-9 months showed evidence of calcineurin inhibitor toxicity in renal biopsy. Isometric vacuolization was seen in all thirteen biopsies, medullary hyalinosis was seen in three of thirteen biopsies and thrombotic microangiopathy in one biopsy.

Alok Sharma25 et al from AIIMS shown that in his 140 protocol biopsy study among kidney transplant recipients, histopathological evidence of toxicity was present in 10.3%, 13.3%, and 5.4% at one month, sixth month and twelve month. Among histological features arterial hyalinosis was significantly correlated feature of CNI toxicity.

Higher number of isometric vacuolization in our study might be due to acute CNI toxicity. Neeraja kampham et al shown that the incidence of CNI toxicity was higher in protocol biopsy over clinically indicated biopsies 41.5% vs 22%.

In our study analysis of trough level vs hypertension, tremor, new onset diabetes, overall clinical toxicity, graft dysfunction and histopathological toxicity were not correlated significantly at 0-3, 3-6, 69 and more than 9 months except trough level versus tremor and overall clinical toxicity at 3-6 and 6-9 months.

In our study there was no significant correlation between clinical toxicity, trough level, graft dysfunction and histopathological correlation at 0-3, 3-6, 6-9 and >9 months.

VII. CONCLUSION

In our study a significant correlation between tremor, clinical toxicity and elevated trough (Co) level at 3-6 and 6-9 month ($P<0.001$) was observed.

There was no significant correlation between clinical toxicity, trough level, graft dysfunction and histopathological correlation at 0-3, 36, 6-9 and >9 months.

There was a significant correlation between tremor and elevated trough level of calcineurin inhibitor was observed at 3-6 and 6-9 months.

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