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Comparative Study of Efficacy of Cyclosporine and Tacrolimus in Renal Transplantation

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Abstract: **Comparison of the use of Cyclosporine and Tacrolimus as primary immunosuppression in renal transplantation at 5years of follow-up by evaluating –**

- **Graft Survival and Patient Survival rate at 6 months, 1 year, 3 years and 5 years between Cyclosporine and Tacrolimus groups.**
- **Survival analysis of patients in Cyclosporine or Tacrolimus groups using Kaplan Meier Survival Curve.**
- **Assessment of Drug induced toxicity in between Cyclosporine and Tacrolimus groups**

Materials & Methods: There were 99 renal transplantations done between 1990-2010.

- **Of these, 97 were Live related kidney transplant and 2 were Cadaver transplant.**
- **52/99 patients fulfilled the inclusion criteria and were included in the study.**
- **Mean Duration of Follow-up was 62.7 months.**

Results: Hypertension was more common in CSA group (89% vs 62.5%, p=0.38)

- **Dyslipidemia was more common in CSA group (55.56% vs 6.25%, p=0.002, Significant)**
- **DGF was more in the TAC group (25% vs 11.11%, p= 0.2005)**
- **Hyperkalemia was more in TAC group (6.25% vs 3%, p=0.857)**
- **NODAT was more common in TAC group (56.25% vs 27.78%, p=0.0348)**
- **At 5 years, the survival rate of graft and patient in the Cyclosporine group was (75% & 80.56%) versus the Tacrolimus group was (87.5% & 87.5%) respectively.**
- **Projected Graft half life in TAC group was 27 yrs versus CSA group of 10.1 years.**

Conclusions: Tacrolimus was more effacious than cyclosporine in terms of allograft survival rate at 5 years of follow up. Also Tacrolimus had fewer side effects as compared to cyclosporine.

Keywords: **Tacrolinmus and Cyclosporine, TAC group.**

1. INTRODUCTION

Tacrolimus was approved for kidney transplantation in 1997. Isolated in 1984 from the fermentation broth of *Streptomyces tsukubaensis***,** a soil organism found at the foot of Mount Tsukuba near Tokyo. Initial clinical trials of tacrolimus as primary immuno-suppressive agent began in Liver transplantation in University of Pittsburgh in 1990. By 2003, 67% of all new kidney transplant recipients and 89% of all new liver transplant recipients were receiving tacrolimus as immunosuppressive therapy **[1,2]**

Cyclosporine (CSA) had been the main stay of immunosuppression in our unit until 2003. We changed to Tacrolimus (TAC) in 2003 as TAC was 10 to 100 times more potent in its immunosuppressive properties.

Aims & Objectives:

- Comparison of the use of Cyclosporine and Tacrolimus as primary immunosuppression in renal transplantation at 5years of follow-up by evaluating Graft Survival and Patient Survival rate at 6 months, 1 year, 3 years and 5 years between Cyclosporine and Tacrolimus groups.
- Survival analysis of patients in Cyclosporine or Tacrolimus groups using Kaplan Meier Survival Curve.

- Estimation of graft half life in each group.
- Assessment of Drug induced toxicity [Tremors, Hypertension, Hyperglycemia, Hyperkalemia, Dyslipidemia] in between Cyclosporine and Tacrolimus groups.

Inclusion Criteria:-

Patients undergoing renal transplant between 1ST January 1990 TO 31ST August 2010 and had a minimum follow-up of one year were included in the study.

Exclusion Criteria:-

- Follow up of less than 1 year.
- Patients on immunosuppression other than Cyclosporine or Tacrolimus.

2. MATERIAL & METHODS

- There were 99 renal transplantations done between 1990-2010.
- Of these, 97 were Live related kidney transplant and 2 were Cadaver transplant.
- 52/99 patients fulfilled the inclusion criteria and were included in the study.
- Mean Duration of Follow-up was 62.7 months.
- In our study, there were 36 patients (62.07%) who received CSA & 16 patients (27.58%) who received TAC as primary immuno suppression .Two patients (3.44%) received other form of immuno suppression for eg. Sirolimus . 4 patients (6.97%) had immediate graft dysfunction & hence the use of immuno suppression could not be tested
- There were 30 males (83.33%) & 6 females (16.67%) in the CSA group & median age at transplant was 34.5 years.
- There were 14 males (87.5%) & 2 females (12.5%) in the TAC group & median age at transplant was 35.8 years.

PROTOCOL OF IMMUNOSUPPRESSION

CSA based

- **CSA + AZA + STEROIDS N = 34**
- **CSA + MMF + STEROIDS N = 2**

TAC based

- **TAC + MMF+ STEROIDS N = 14**
- **TAC +AZA+ STEROIDS N = 1**
- **TAC+ STEROIDS N = 1**
- Cyclosporine was started 5mg/kg/day on Day -4
- CSA group – C0 & C2 levels aimed at :-

	0-1 month	1-6 months	> 6 months
C0 (µg/dl)	200-300	150-250	100-200
C2 (µg/dl)	1500-1800	1000-1500	600-1000

- Azathioprine was started as 3 mg/kg/day on Day -2,titrated as per WBC counts.
- Tacrolimus was started 0.15mg/kg/day Day -4
- TAC group – T0 levels aimed at :-

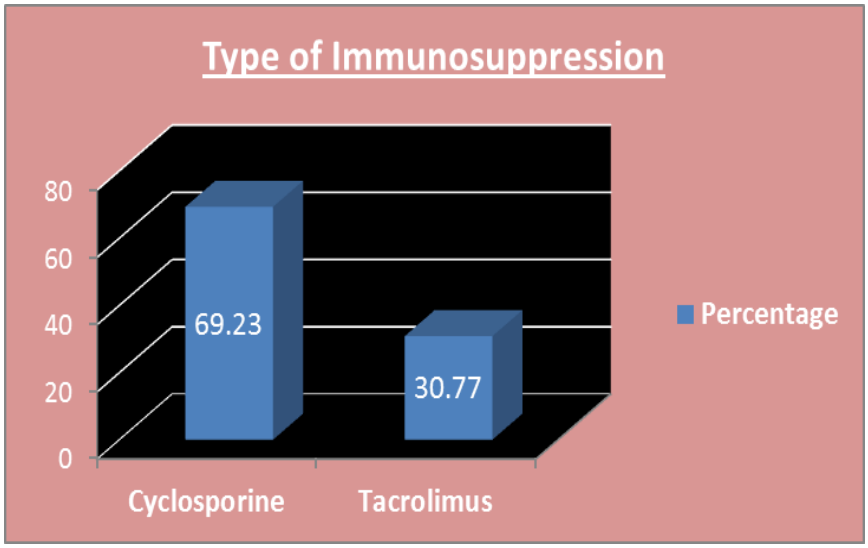
	0-1 months	1-3 months	4-6 months	> 6 months
T0 (ng/dl)	10-12	8-10	5-8	3-5

- Mycophenolate mofetil was started as 1.5gm/day on Day -2,titrated as per WBC counts

3. STATISTICAL ANALYSIS

- Data entry was done in Excel, analysis is done with the help of SPSS Version 15 and Medcal Version 9 software.
- Percentage and Frequency tables were used for presentation of results.
- Survival of graft and patient was calculated by Kaplan Meir survival curve and for comparison between study group Log rank regression test was used.
- P value less than 0.05 was taken as significant level.

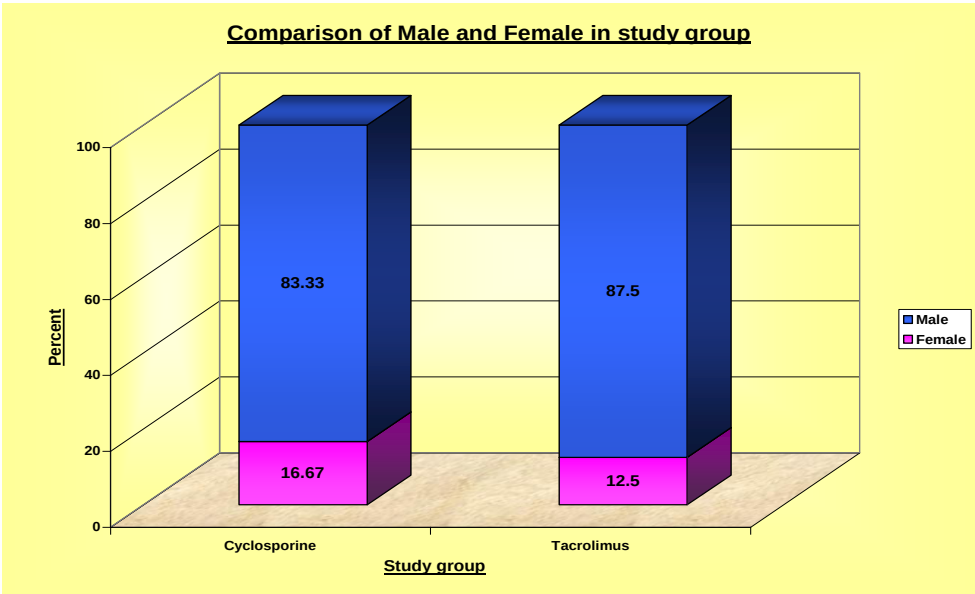
TABLE 1



Immunosuppressant	No. of Patients	Percent
Cyclosporine	36	69.23
Tacrolimus	16	30.77
Total	52	100

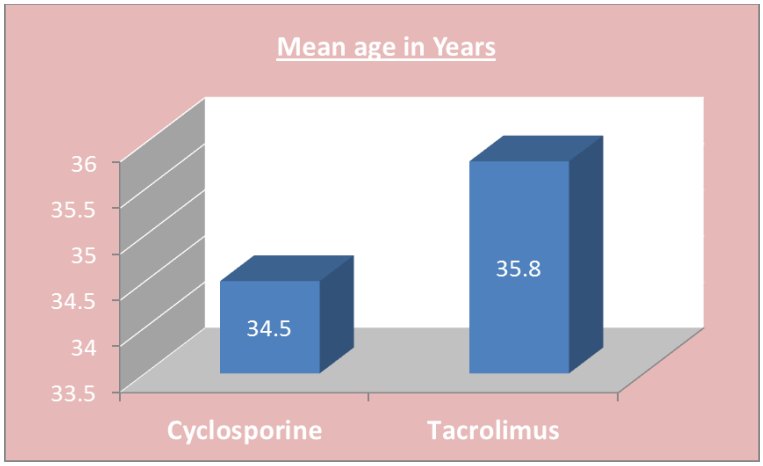
TABLE 2: GENDER CHARACTERISTICS

Males were 48 [84.48%] and Females were 9 [15.52%]



	Males	Percent	Females	Percent
Cyclosporine	30	83.33	6	16.67
Tacrolimus	14	87.5	2	12.5

TABLE 3: AGE



Mean age for Males was 35.7 years and Females was 29.3 years

TABLE 4: DONOR CHARACTERISTICS

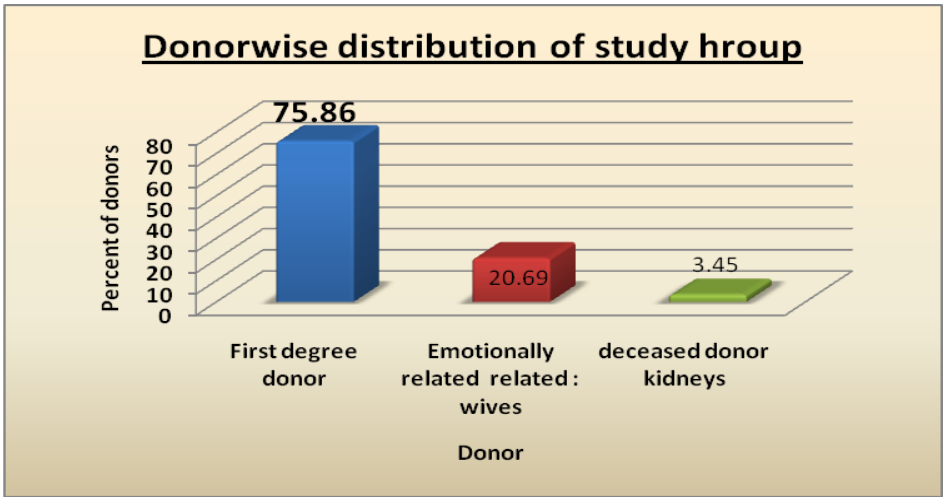
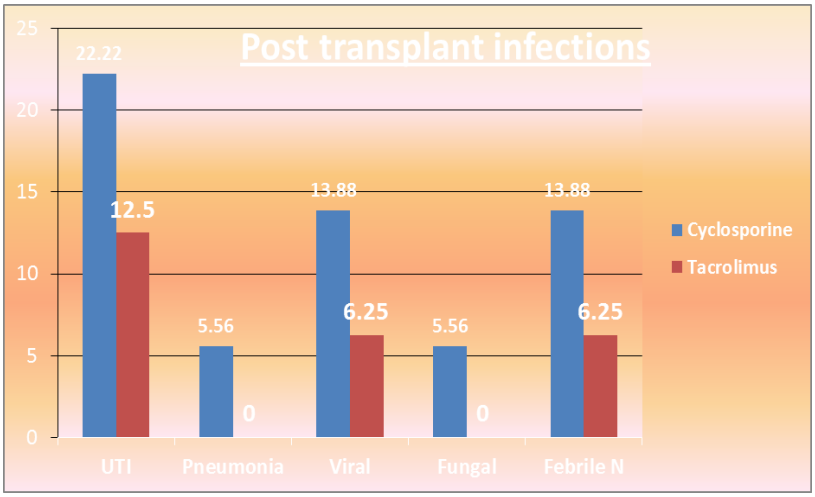


TABLE 5: POST TRANSPLANT INFECTIONS



Post op infections	CSA		TAC		Chi-square (df=2)	p value
	No of pt	Percent	No of pt	Percent		
UTI	8	22.22	2	12.5		
Pneumonia	2	5.56	0	0		0.3312
Viral	5	13.88	1	6.25		
Fungal	2	5.56	0	0	9.441	
Febrile N	5	13.88	1	6.25		Associtn is not signf
No infections	14	38.89	12	75		
Total	36	100	16	100		

Infections were very commonly encountered. 9 patients[15.50%] had Urinary tractinfection [UTI], 2 patients [3.44%] had Pneumonia [PCP] 3 patients [5.1%] had viral infections either in the form of Herpes Zoster [2patients] and Varicella [1patient] Fungal infections were present in 3 patients [5.16%] in the form of oral candidiasis, UTI in 1patient [1.72%] and invasive aspergillosis 1 patient [1.72%]. Skin lesions were present in 5 patients [8.6%]. Dangerous febrile neutropenia was present in 4 patients[6.9%] and in those patients who recieved induction therapy with Thymoglobulin or Daclizumab.

Surgery related complications included wound leak in 1 patient [1.72%], ureteric leak in 1 pt [1.72%], lymphocoele requiring drainage in 3 patients [5.16%].

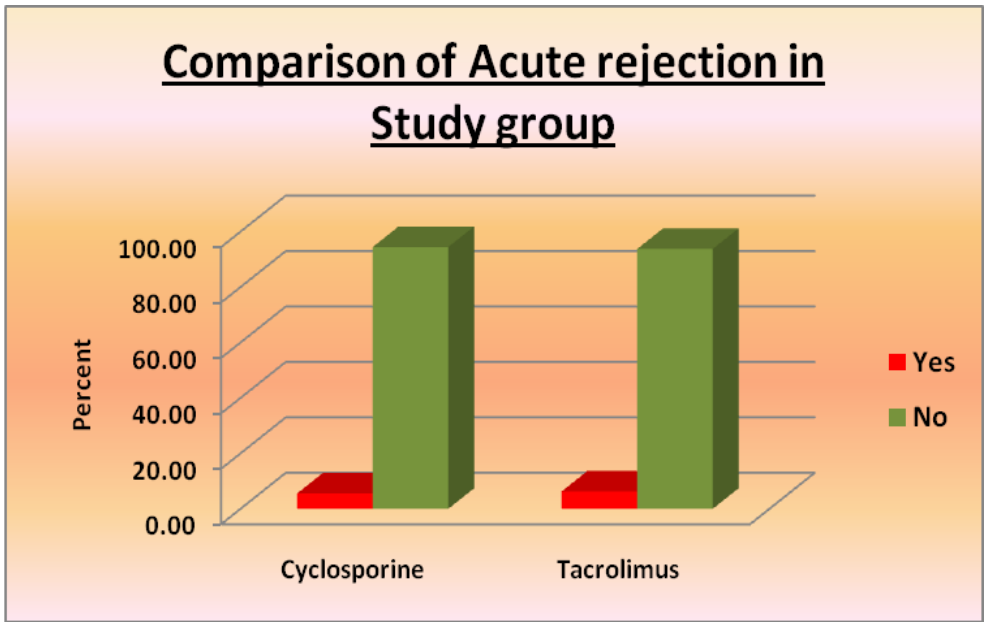
RARE POST TRANSPLANT INFECTION-

Among 10 Laparoscopic Nephrectomy, we had Atypical Mycobacterial infection at surgical incision site in 9 patients [15.48%], commonest organism was ***Mycobacterium Fortuitum***, as cultured from the pus from the incision site.

All these infections were tracked to the infected Laparoscope used for donor nephrectomy, the source of infection being the 2% glutaraldehyde solution in which the instrument was kept for dis-infection. The Hospial infection committee immediately took measures to combat the source and prevent future incidences of atypical mycobacterial infections. The infected renal allograft recipients were treated with modified AKT comprising of Clarithromycin, Co-trimoxazole, Linezolid, Ciprofloxacin as per the culture sensitivity report. The duration of treatment was one year. At present all the patients are asymtomatic and their skin lesions and peri-nephric collection have healed

TABLE 6: ACUTE REJECTION IN THE STUDY GROUP

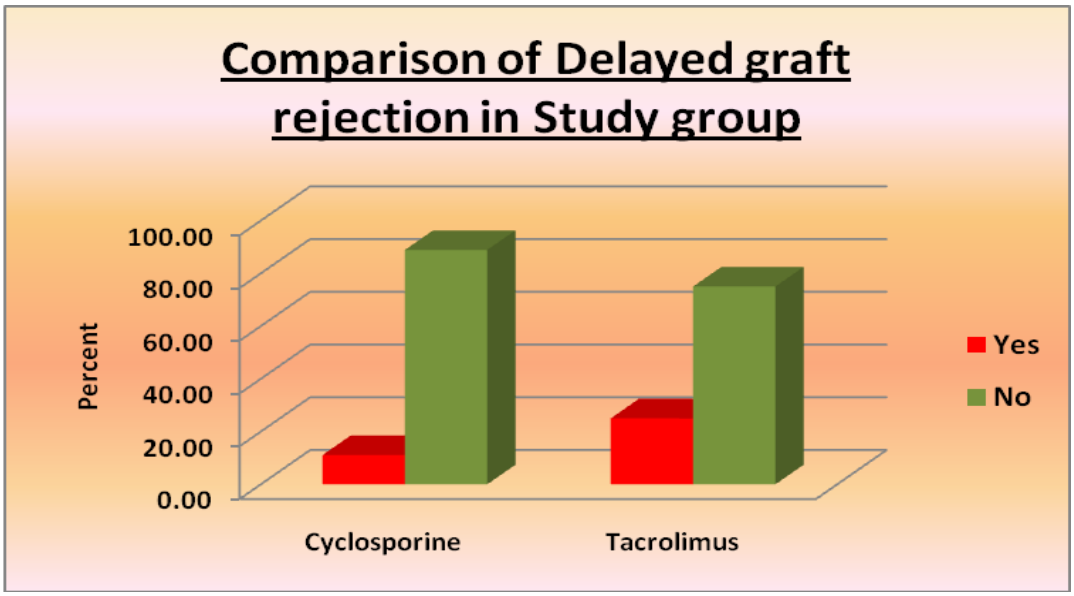
The rate of acute rejection was comparable between the two groups. In Cyclosporine group, acute rejection was 5.5% while it was 6.0% in the Tacrolimus group.



Acute rejection	Cyclosporine		Tacrolimus		Total	Chi-square	p value
	Number of patients	Percent	Number of patients	Percent			
Yes	2	5.56	1	6.25	3	0.2972	0.5856
No	34	94.44	15	93.75	49		Not significant
Total	36	100	16	100	52		

TABLE 7: COMPARISON OF DELAYED GRAFT REJECTION

There was a higher incidence of Delayed Graft Function with the use of tacrolimus (25%) as compared to cyclosporine (11.11%) in our study.



Delayed graft rejection	Cyclosporine		Tacrolimus		Total	Chi-square	p value
	Number of patients	Percent	Number of patients	Percent			
Yes	4	11.11	4	25	8	0.7479	0.2005
No	32	88.89	12	75	44		Not significant
Total	36	100	16	100	52		

TABLE 8: DRUG TOXICITY

A) Among the drug induced toxicities, In Tacrolimus group, 4 patients [6.90%] had tacrolimus toxicity in the form of tremors, rising serum creatinine, and hyperkalemia. 1 patient had tacrolimus related Hemolytic-Uremic Syndrome which resolved on stopping the drug.

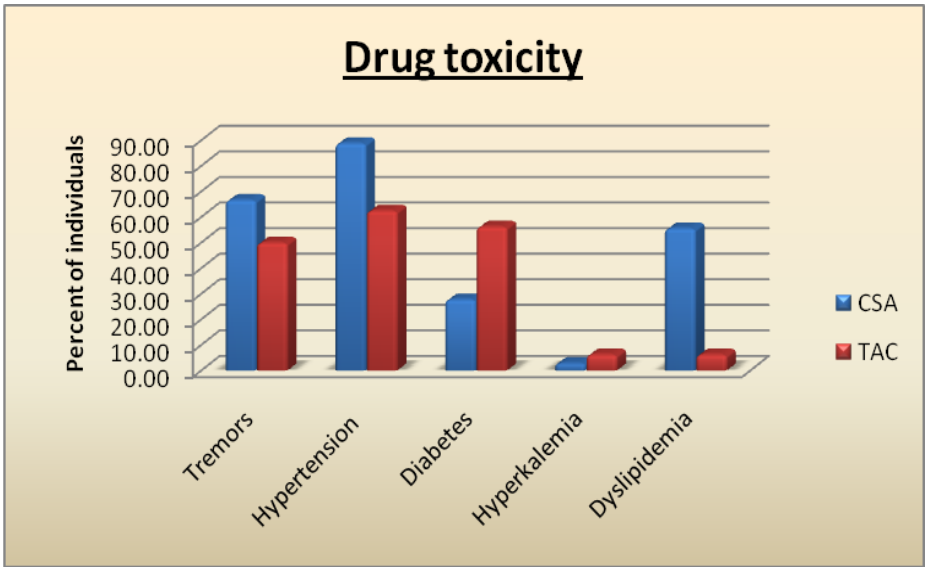
B) Cyclosporine Toxicity was present in 5 patients [8.6%] including tremors, hirsutism, gum hypertrophy.

C) 4 patients recieving Mycophenolate mofetil had transient leucopenia, 4 patients recieving Azathioprine [6.9%] had transient leucopenia which resolved on reduction of dose.

D) New onset Diabetes after transplant [NODAT] was present in 20/58 patients [34.5%] requiring insulin therapy in the immediate post transplant period. NODAT was seen in Cyclosporine (28%) as compared to tacrolimus (56%).Hypertension was more common in CSA group 88.88% as compared to TAC group 62.5% patients.

E) Hypertension was present in 42/58 patients [72.41%] post renal transplant requiring anti-hypertensives. Hypertension was more common in CSA group 88.88% as compared to TAC group 62.5% patients.

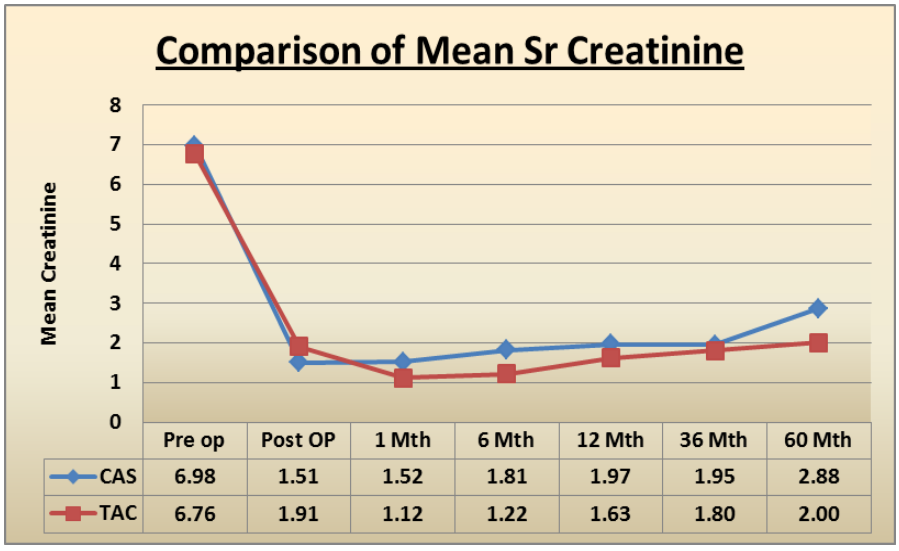
F) Hyperkalemia was present in 5 % patients. Hyperkalemia was more common in patients taking tacrolimus (6%) than cyclosporine (3%)



Drug toxicity	CSA		TAC		Chi-square (df=2)	p value
	Number of patient	Percent	Number of patient	Percent		
Tremors	24	66.67	8	50	10.36	0.0348
Hypertension	32	88.89	10	62.5		
Diabetes	10	27.78	9	56.25		
Hyperkalemia	1	2.78	1	6.25		Association is not significant
Dyslipidemia	20	55.56	1	6.25		

TABLE 9: COMPARISON OF MEAN SERUM CREATININE

The mean serum creatinine was comparable in the two groups. At the end of 60 months, the mean serum Creatinine in the Tacrolimus group is 2 mg%, and in the Cyclosporine group is 2.88 mg%



p= 0.828 mean difference is not significant

SURVIVAL ANALYSIS:

The survival analysis for CSA & TAC was done by using Kaplan- Meier curve

The graft & patients survival were recorded at 1 month, 6 month, 36 month, 60 month post transplant.Maximun follow up for the CSA group was 180.9 months and that of TAC group was 63.3 months

Among the CSA (36 pts) & the TAC group (16 pts), In CSA group median graft survival is 166.5 months. In the TAC group median graft survival is 36.83 months. In CSA group median patient survival is 48.48 yrs. In the TAC group median patient survival is 51.5 yrs. Using Log Rank (Mantel-Cox) test & applying chi- square test, there is no difference between median patient survival in either CSA or TAC group (p=0.290,not significant).

TABLE 10: KAPLAN-MEIER SURVIVAL CURVE FOR ALLOGRAFT

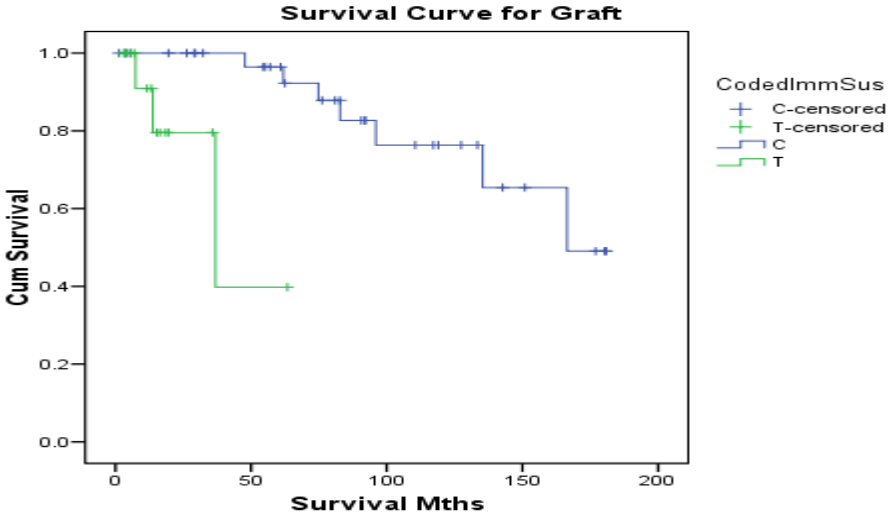


TABLE 11: KAPLAN-MEIER SURVIVAL CURVE FOR PATIENT SURVIVAL

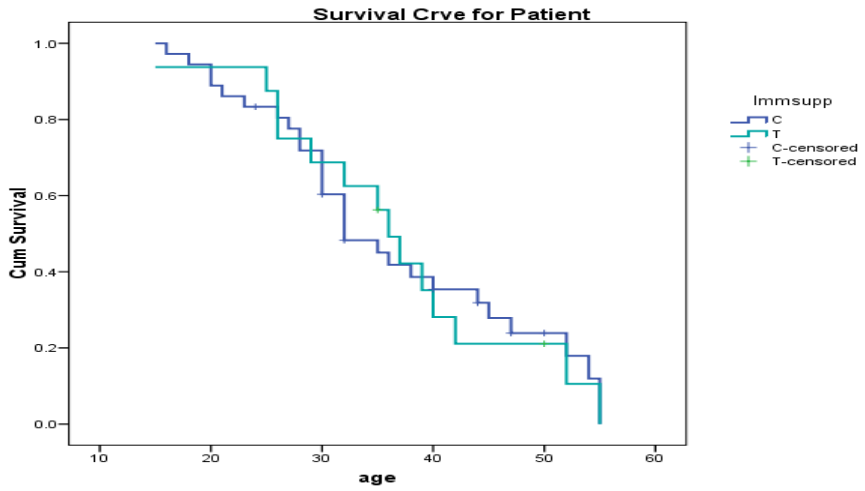


TABLE 12: PROJECTED GRAFT HALF-LIFE IN YEARS IN TACROLIMUS GROUP

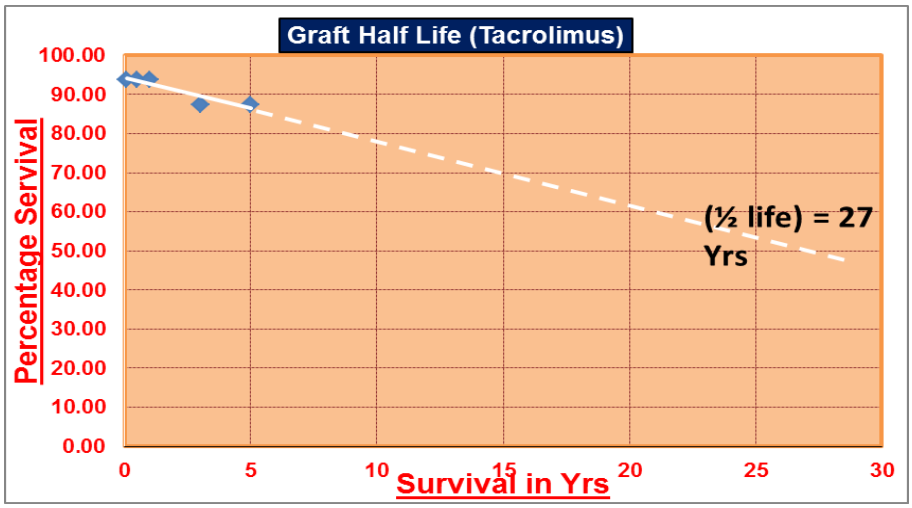


TABLE 13: PROJECTED GRAFT HALF-LIFE IN YEARS IN CYCLOSPORINE GROUP

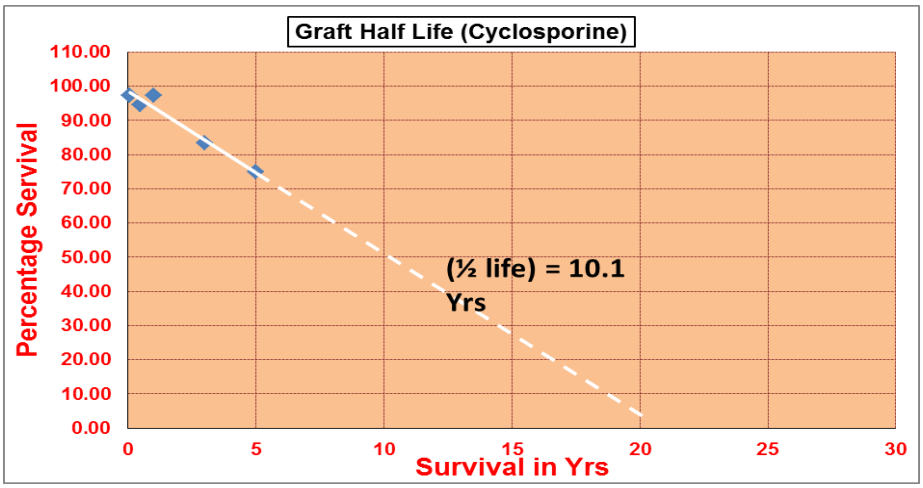


TABLE 14: COMPARISON OF GRAFT SURVIVAL RATE BETWEEN CYCLOSPORINE AND TACROLIMUS GROUPS

The Graft survival rate of renal allograft recipients in CSA and TAC group was compared at 1 month, 6 months, 12 months, 36 months and 60 months.It was found that at the end of 60 months, the graft survival rate was higher in the TAC group [87.5%] as compared to graft survival in CSA group [75%]

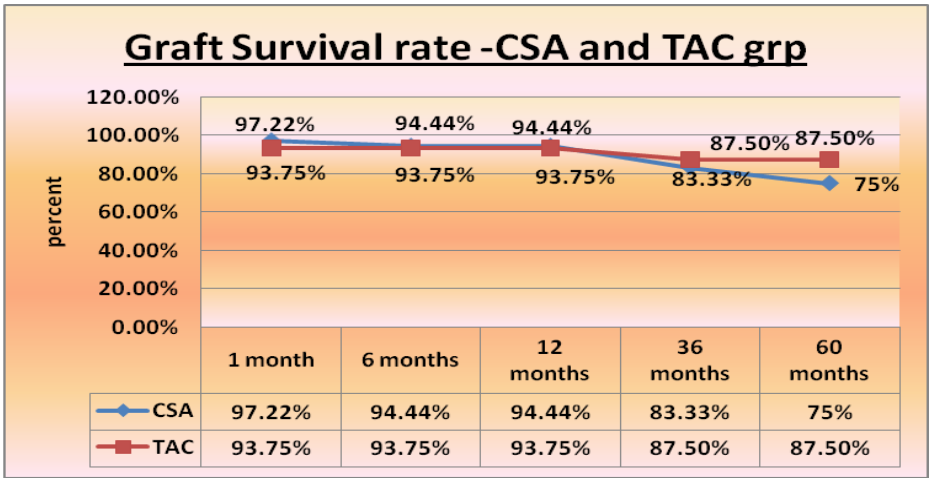
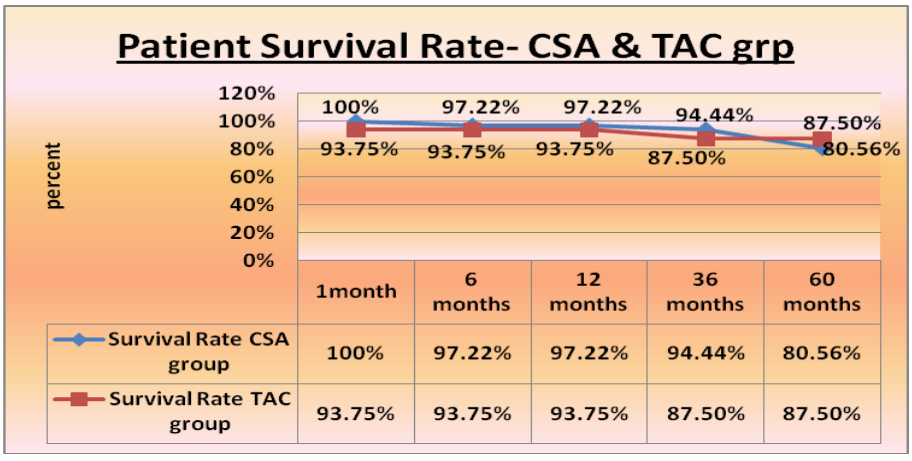


TABLE 15: COMPARISON OF PATIENT SURVIVAL RATE BETWEEN TACROLIMUS AND CYCLOSPORINE GROUPS

The Patient survival rate of renal allograft recipients in CSA and TAC group was compared at 1 month, 6 months, 12 months, 36 months and 60 months.It was found that at the end of 60 months, the patient survival rate in the TAC group [87.5%] as compared to graft survival in CSA group [80.56%]



4. RESULTS

- Hypertension was more common in CSA group (89% vs 62.5%, p=0.38)
- Dyslipidemia was more common in CSA group (55.56% vs 6.25%, p=0.002, Significant)
- DGF was more in the TAC group (25% vs 11.11%, p= 0.2005)
- Hyperkalemia was more in TAC group (6.25% vs 3%, p=0.857)
- NODAT was more common in TAC group (56.25% vs 27.78%, p=0.0348)
- At 5 years, the survival rate of graft and patient in the Cyclosporine group was (75% & 80.56%) versus the Tacrolimus group was (87.5% & 87.5%) respectively.
- Projected Graft half life in TAC group was 27 yrs versus CSA group of 10.1 years
- In CSA group median graft survival is 166.5 months. In the TAC group median graft survival is 36.83 months. In CSA group median patient survival is 48.48 yrs. In the TAC group median patient survival is 51.5 yrs. Using Log Rank (Mantel-Cox) test & applying chi- square test, there is no difference between median patient survival in either CSA or TAC group (p=0.290,not significant).

5. DISCUSSION

Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD). Strategies to increase donor organ availability and to prolong the transplanted kidney's survival have become priorities in kidney transplantation. Standard immunosuppressive therapy consists of initial treatment and maintenance regimes to prevent rejection and short courses of more intensive immunosuppressive therapy to treat episodes of acute rejection.

We present clinical profile and demography of patients undergoing renal transplant in a tertiary care centre. We have analyzed these patients as regards their post-transplant course, immediate post-transplant complications, their follow up assessment at 6 months, one year, 3 years and five years. The long term complications, graft and patient survival at five years was calculated by Kaplan-Meier analysis. Further, our study compared tacrolimus and cyclosporine used as primary immunosuppression for kidney transplant recipients and their effect on respective patient and survival rate.

Tacrolimus was shown to be superior to cyclosporine in improving graft survival but increases post-transplant diabetes.

Immunosuppressive treatment with tacrolimus has proven efficacy in short-term clinical outcomes. The excellent results obtained in preventing rejection in the short term have shifted the focus of clinical research to the evaluation of the long-term efficacy and safety of maintenance treatment with tacrolimus and ciclosporin A microemulsion (CsA-ME).

The results of clinical studies have shown comparable longer-term patient and graft survival with tacrolimus and CsA-microemulsion. For example, a US comparative study **[3]** showed equivalent patient and graft survival at 3 years with tacrolimus or CsA-microemulsion maintenance immunosuppression and a multivariate analysis of retrospective US Renal Transplant Scientific Registry data **[4]** demonstrated that both Tacrolimus and CsA-microemulsion conferred approximately equal protection against the risk of graft loss secondary to chronic allograft failure at 4 years. However, at 5 years, the projected graft half-life was longer, and chronic rejection was less frequent with tacrolimus-based immunosuppression **[5].** And, results of a longer-term European comparative study **[6]** demonstrated better 6-year graft survival and longer estimated graft half-life with tacrolimus.

In terms of safety, clinical research results indicate advantages with maintenance tacrolimus. In three separate comparative studies, longer-term renal function, as measured by serum creatinine, was lower at 3 years **[3]** in patients maintained on tacrolimus, and glomerular filtration rate (GFR) was better with tacrolimus at 5 years **[7]** and at 6 years **[6]**.

The aim of this observational follow-up study was to evaluate the clinical outcome at 60 months post-transplant in terms of the rate of acute rejection, graft and patient survival and renal allograft function.

In this follow-up of the first Indian clinical trial in kidney transplantation to compare the efficacy and safety of a tacrolimus-based regimen with ciclosporin, we found similar efficacy outcomes in the two treatment groups during the 36- to 60-month study period. Further, rates of graft loss at 36 months were comparable between groups. We found advantages with respect to longer-term tacrolimus treatment over cyclosporine.We found a better graft survival rate for tacrolimus as compared to cyclosporine when compared at 60 months .

In the present study, renal function was comparable in the two treatment groups. Results of a 5-year US multicentre comparative study showed significantly higher serum creatinine in patients maintained on cyclosporine compared with tacrolimus **[7].** Other studies have shown an improvement in serum creatinine when cyclosporine-ME is either withdrawn or replaced **[10,11]** . In a recent systematic Cochrane review, that analyzed 4102 renal transplant recipients **[12]**, it has been reported that graft survival as well as renal function is superior with tacrolimus-based immunosuppression compared to cyclosporine-based immunosuppression, thereby confirming and extending the results of several prospective randomized trials **[3,5,6,7,8,9].**

There was a higher incidence of Delayed Graft Function with the use of tacrolimus (25%) as compared to cyclosporine (11.11%) in our study. However the rate of acute rejection was comparable between the two groups. In Cyclosporine group, acute rejection was 5.5% while it was 6.0% in the Tacrolimus group.

NODAT was seen in Cyclosporine (28%) as compared to tacrolimus (56%).

Hyperkalemia was also more common in patients taking tacrolimus than cyclosporine.

We found more number of hypertension in the cyclosporine treatment group. A similar comparative study **[6]** found significant differences between tacrolimus and cyclosporine-ME in regard to cardiovascular risk factors at 3 years. At 5-year follow-up, a US comparative study showed a significantly greater use of antihypertensive medications and serum lipid lowering medications with cyclosporine compared with tacrolimus **[7].** There may be a link between hypercholesterolemia and an increased risk of late graft loss in patients with at least one episode of acute rejection as suggested by the results of one study **[13]** .

We had higher number New Onset Diabetes Mellitus (NODAT) in the tacrolimus group. These findings are consistent with studies demonstrating increase incidences of NODAT after use of tacrolimus.

6. LIMITATIONS OF THE STUDY

- A potential limitation of the present analysis is that the follow-up study sample was limited to 60% of the original cohort; 39 patients who received renal transplant between 1990- 2001 did not participate in follow-up.(These patients received CSA+ AZA+ Prednisolone)
- However, the percentage of the original sample that was available for our follow-up analysis is in line with that used in the analysis of other long-term studies **.[3,7]**
- 75% of the donors are first degree relatives. Impact of TAC on long term outcome of unrelated [not first degree relatives] could not be addressed to.
- A long term analysis over 10 years is warranted to assess risk Vs benefit of Tacrolimus.

REFERENCES

[1] Shapiro R, Young JB, Milford EL, et al: Immunosuppresion: Practices and Trends.1993-2003, Am Jr Transplant: 5:874, 2005.

[2] Todo S, Fung JJ, Starzl TE, et al, Liver, Kidney and Thoracic organ transplantation under FK-506, Ann Surg 212: 295, 1990.

[3] Gonwa T, Johnson C, Ahsan N, et al. Randomized trial of tacrolimus + mycophenolate mofetil or azathioprine versus cyclosporine + mycophenolate mofetil after cadaveric kidney transplantation: results at three years. Transplantation (2003) 75:2048–2053.

[4] Meier-Kriesche HU, Kaplan B. Ciclosporin microemulsion and tacrolimus are associated with decreased chronic allograft failure and improved long-term graft survival as compared with Sandimmune. Am J Transplant (2002) 2:100–104.

[5] Mayer AD. for the European Tacrolimus Multicentre Renal Study Group. Chronic rejection and graft half-life: five-year follow-up of the European tacrolimus multicenter renal study. Transplant Proc (2002) 34:1491–1492.

[6] Jurewicz WA. Tacrolimus versus ciclosporin immunnosuppression: long-term outcome in renal transplantation. Nephrol Dial Transplant (2003) 18(Suppl_1):7–11.

[7] Vincenti F, Jensik SC, Filo RS, et al. A long-term comparison of tacrolimus (FK506) and ciclosporin in kidney transplantation: evidence for improved allograft survival at five years . Transplantation (2002) 73:775–782.

[8] Radermacher J, Meiners M, Bramlage C, et al. Pronounced renal vasoconstriction and systemic hypertension in renal transplant patients treated with cyclosporin A versus FK 506. Transpl Int (1998) 11:3–10.

[9] Solez K, Axelsen RA, Benediktsson H, et al. International standardization of criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. Kidney Int (1993) 44:411–422.

[10] Johnson RWG, Kreis H, Oberbauer R, et al. Sirolimus allows early ciclosporin withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. Transplantation (2001) 72:777–786.

[11] Groth CG, Baeckman L, Morales JM, et al. for the Sirolimus European Renal Transplant Study Group. Sirolimus (Rapamycin)-based therapy in human renal transplantation. Similar efficacy and different toxicity compared with ciclosporin. Transplantation (1999) 67:1036–1042.

[12] Webster AC, Woodroffe RC, Taylor RS, et al. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. Br Med J (2005) 331:810–820.

[13] Wissing KM, Abramowicz D, Broeders N, et al. Hypercholesterolemia is associated with increased kidney graft loss caused by chronic rejection in male patients with previous acute rejection. Transplantation (2000) 70:464–472.