

Study to develop Alternate Sampling Strategies to measure tacrolimus and creatinine – to facilitate the domiciliary care of renal transplant patients: an interim analysis

Binu Susan Mathew, Sumith Mathew, Santosh Varughese*, David VG*, Jeyaseelan L\$, Melvin Joy\$, Ratna Prabha, Blessed Winston, John GT#

-Dept. of Pharmacology and Clinical Pharmacology, Christian Medical College, Vellore, Tamil Nadu, India, * - Dept. of Nephrology, CMC, Vellore, India, \$ - Dept. of Biostatistics, CMC, Vellore, India, # - Kidney Health Service, Royal Brisbane and Women's Hospital, Brisbane, Australia

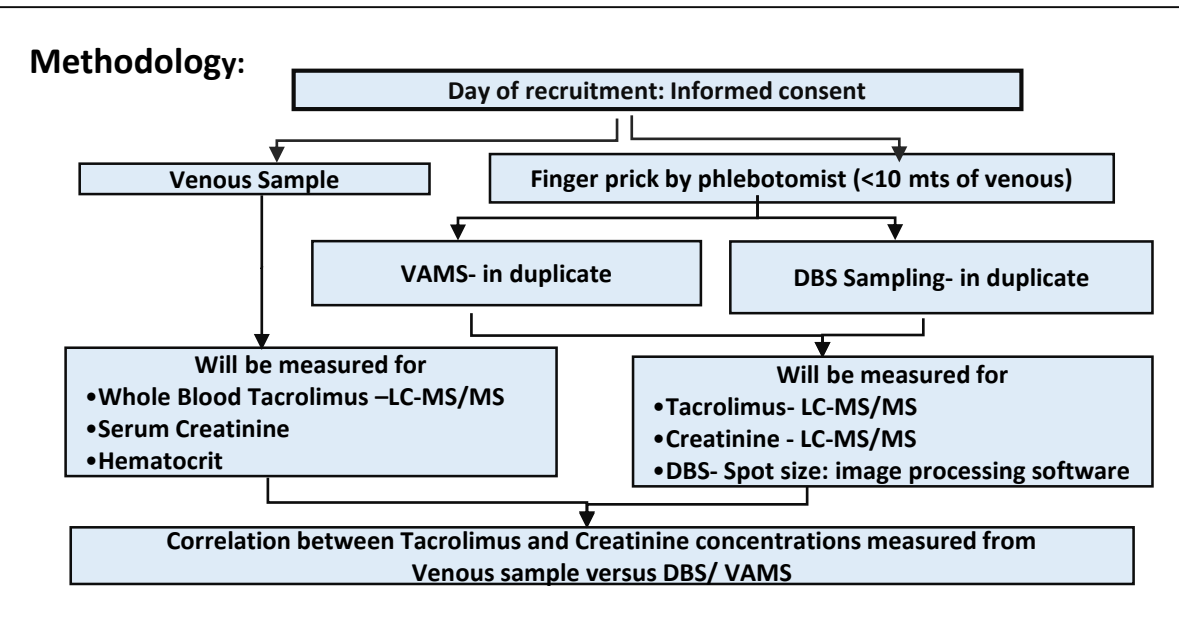


Introduction: Challenges in management of renal transplant patients include:

- Life long requirement of immunosuppressants. Periodic monitoring of renal function and therapeutic drug monitoring of immunosuppressants, to facilitate dose adjustments.
- Facilities to do TDM are limited in the country.
- Regular visits to the nodal transplant centres, which are situated hundreds of miles away from home
- Huge financial burden for travel, stay and loss of work during these visits
- Travel restrictions during a pandemic.

Aims:

- To check the correlation of concentrations of tacrolimus and creatinine, sampled using both, DBS and VAMS methods against whole blood/serum concentrations..
- To study if hematocrit and spot size can be used to predict serum concentrations when measured by DBS.
- If required, to determine the quantum of correction factor required while predicting whole blood/ serum concentrations from both, DBS and VAMS.



ALTERNATE SAMPLING STRATEGIES- studied in this research were collected in duplicate

Mitra® Microsampler (Neoteryx®)
Volumetric Absorptive microsampling (VAMS™)



WHATMAN™ 903 Filter paper
Dried blood spot (DBS)



9 mm disc was punched from the DBS for extraction

Ref:
1. Anal Bioanal Chem (2015) 407:1585–94
2. Bioanalysis (2019) 11(6): 495-508

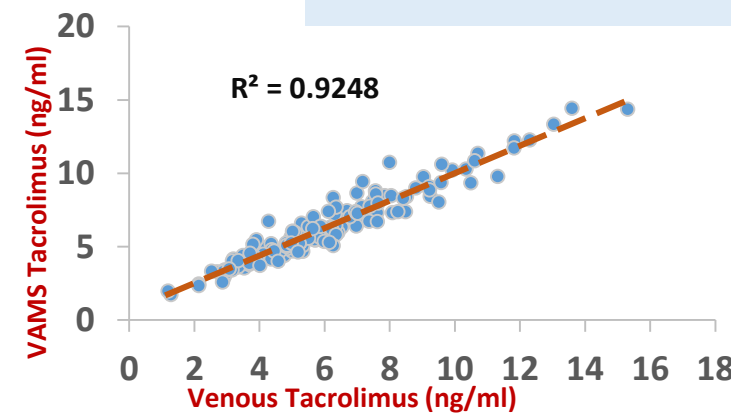
Results : LC- MS/MS assay was developed using a two step extraction technique for both tacrolimus and creatinine. ^{1,2} Both assays were performed with the same extracted sample, for each of the sampling strategies.

Total no. of patients recruited = 152
No. of samples that were analyzed - DBS 1 = 141, DBS 2 = 131
- VAMS 1 = 151, VAMS 2=148

Samples were not analysed because they could not be collected / the spot size was inadequate for analysis

MEAN (sd) of the measured concentrations

	Venous sample (N=152)	DBS (N=148)	VAMS (N=151)
TACROLIMUS	6.2 (2.4)	6.7 (2.9)	6.0 (2.5)
CREATININE	1.37 (0.53)	1.14 (0.46)	1.15 (0.5)



TACROLIMUS	N	ICC	95% CI
Venous vs DBS	148	0.97	0.93-0.98
Venous vs VAMS	151	0.98	0.96-0.99
CREATININE	N	ICC	95% CI
Serum vs DBS	148	0.913	0.21-0.97
Serum vs VAMS	151	0.926	0.39-0.98

Intraclass correlation (ICC):
Agreement between the gold standard with DBS and with VAMS

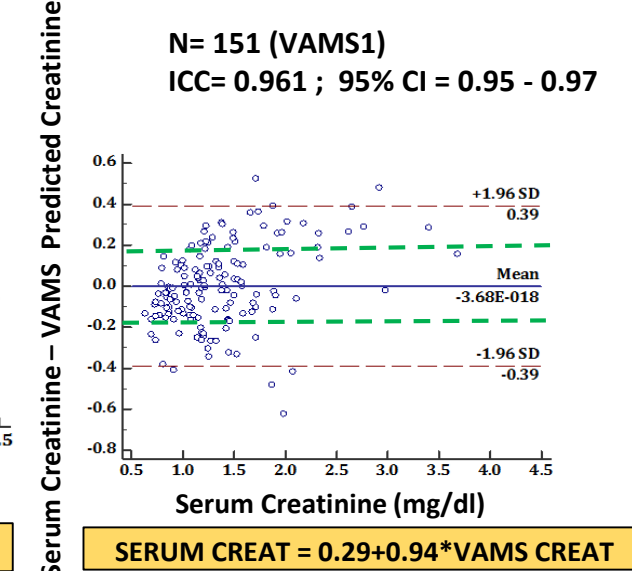
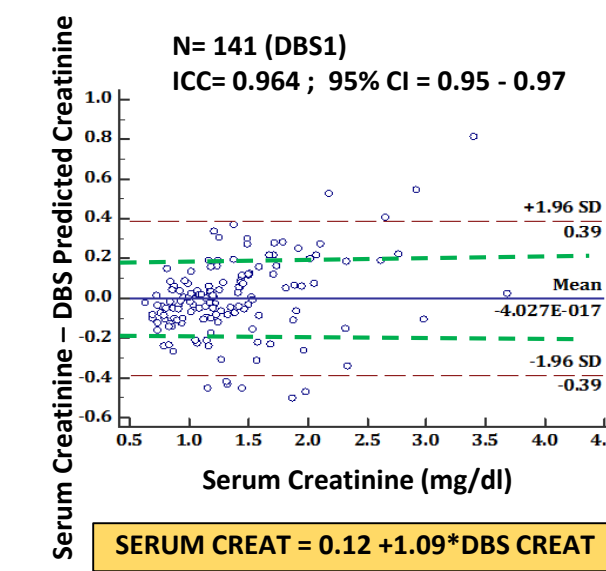
TACROLIMUS	N	ICC	95% CI
DBS 1 vs DBS 2	124	0.99	0.98-0.99
VAMS 1 vs VAMS 2	148	0.97	0.96-0.98
CREATININE	N	ICC	95% CI
DBS 1 vs DBS 2	124	0.97	0.96-0.98
VAMS 1 vs VAMS 2	148	0.96	0.94-0.97

Intraclass correlation (ICC):
Agreement between the duplicate samples for both, DBS and VAMS

N=141	p value
DBS CREAT1	<0.001
Adjusted R ² of the model	0.87
N=141	p value
DBS CREAT1	<0.001
Spot size	0.071
Hematocrit	<0.001
Adjusted R ² of the model	0.88
N=151	p value
VAMS CREAT1	<0.001
Adjusted R ² of the model	0.86

Regression Analysis

- Spot size of the DBS and hematocrit are significant predictors of serum creatinine.
- Adjusted R² did not improve when spot size and hematocrit were included in the multiple linear regression analysis.
- DBS and VAMS creatinine were equally effective in predicting serum creatinine.



Conclusions:

- DBS and VAMS are equally effective to measure tacrolimus concentration
- No influence of hematocrit and spot size on the DBS creatinine prediction.
- DBS and VAMS are equally effective to predict serum creatinine.
- Prediction of serum creatinine from DBS or VAMS is clinically useful but should be interpreted with caution
- VAMS creatinine, together with tacrolimus, using finger prick sample – is a first time approach.

Acknowledgements: Ms Daisy, Mr Madan, Mr Naveen G, Mr Subash & IRB of CMC. To Science and Engineering Research Board, DST, Govt. of India for funding this research.