Capillary versus Venous Therapeutic Drug Monitoring of Tacrolimus and Cyclosporine A

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Abstract

Background: Following allogeneic organ transplants, patients are placed on immunosuppressive drugs (e.g., Tacrolimus [Tac] or Cyclosporine A [CsA] to lower the risk of organ rejection). These medications have a narrow therapeutic window where too little drug may lead to organ rejection, but too high of a concentration can lead to adverse drug reactions and organ damage. Unfortunately, laboratory assays for these medications are not harmonized, so results for Tac and/or CsA may be vastly different even if the two labs use the same methodology (i.e., LC-MS/MS).[1] Therefore, this study examined the use of the Mitra® microsampling collection devices (Neoteryx) so that in the future, patients could self-collect a capillary sample from their home or remote clinical site. A total of 50 patients taking Tac and 45 patients taking CsA were compared. The study also examined the stability of the dried blood samples and overall patient satisfaction with the capillary blood collection process.

Methods: After Mayo Clinic IRB approval was obtained, 50 patients prescribed Tac and 45 patients prescribed CsA were enrolled and consented into the study. The patients were instructed on how to perform the capillary collection and observed or assisted if necessary when two microsampling devices (20 µL whole blood per device) were collected immediately prior to or after their venous blood draw. All the samples were then sent to the clinical laboratory where they were analyzed using a High-Performance Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS) test that was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. The patients also completed a short satisfaction survey on the capillary collection experience. In addition, microsampling devices were spotted using freshly collected de-identified residual blood pooled from patients taking Tac and CsA. Three pools across the analytical measuring range were made and spotted on microsampling devices for each immunosuppressant. The devices were then stored at room temperature in foil pouches and tested in duplicate on day 1, 3, 7, 14, and 28 for comparison to the original value.

Results: Stability studies showed CsA dried blood spots were stable for up to 7 days at room temperature with an average difference of <10% (actual 5.7%), but subsequent testing showed >20% difference on days 14 and 28. Tac dried blood spots showed more variability, but were stable up to 3 days and exceeded 20% difference on day 7-28. Capillary versus venous blood collection results showed good correlation but there was a negative bias with the capillary collections for both CsA (slope = 0.923 R^2=0.894) and Tac (slope = 0.840 R^2=0.824). This bias likely was caused by the milking of the finger during the capillary collection process. Finally, the patient survey's showed an overwhelming 83.2% of the patients preferred the capillary collection option with the ability to collect future samples at home while 12.6% had no preference and 4.2% preferred to still go to a phlebotomy draw site for a venous collection.

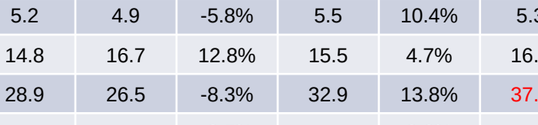
Conclusions: In the end, this project showed decent correlation between capillary and venous blood draw samples for Tac and CsA. A larger correlation and stability study would need to be performed to verify the results and ability to collect samples at home and mail them back to the laboratory. However, if successful this new protocol would allow less blood to be collected (20 µL vs 4 mL whole blood) which is important especially in pediatric transplant patients. This process would also allow physicians/pharmacists the ability to serially monitor patients on Tac or CsA more consistently using the same laboratory, reduce shipping costs and improve patient satisfaction.

Study Aims

1. To assess if dried blood collected using a finger stick (capillary collection) and Mitra microsampling collection device correlated to venous collected blood (traditional phlebotomy) to monitor the trough concentrations of tacrolimus or cyclosporine A.
2. To assess patient satisfaction of using a capillary finger stick and microsampling collection device for monitoring Tac or CsA.

Methods

- Consent 50 patients taking tacrolimus and 45 patients taking cyclosporine A
- Collect trough immunosuppressant level using both a 20 µL Mitra microsampling device and traditional venous blood draw



- Measure Tac or CsA concentrations by LC-MS/MS (Agilent RapidFire with 6495) using the 20 µL dried capillary blood vs. 200 µL venous EDTA whole blood
- Perform stability studies with Mitra microsampling devices spotted (20 µL), stored at room temperature in foil pouches, and tested in duplicate on day 1, 3, 7, 14, and 28 by LC-MS/MS
- Collect patient satisfaction data using survey

Stability Data

Ambient:

CsA	Day 0 (ng/mL)	Day 1 (ng/mL)	Day 1 % Diff	Day 3 (ng/mL)	Day 3 % Diff	Day 7 (ng/mL)	Day 7 % Diff
Low	115	106	-7.8%	127	10.4%	111	-3.5%
Med	312	280	-10.3%	342	9.6%	344	10.3%
High	521	528	1.3%	560	7.5%	574	10.2%
Avg			-5.6%		9.2%		5.7%

Tac	Day 0 (ng/mL)	Day 1 (ng/mL)	Day 1 % Diff	Day 3 (ng/mL)	Day 3 % Diff	Day 7 (ng/mL)	Day 7 % Diff
Low	5.2	4.9	-5.8%	5.5	10.4%	5.3	1%
Med	14.8	16.7	12.8%	15.5	4.7%	16.4	10.8%
High	28.9	26.5	-8.3%	32.9	13.8%	37.5	29.9%
Avg			-0.5%		9.6%		13.9%

Acceptance Criteria: Average % Difference <10%; no one value >20%

Patient Survey Data

What collection method would you prefer in the future?

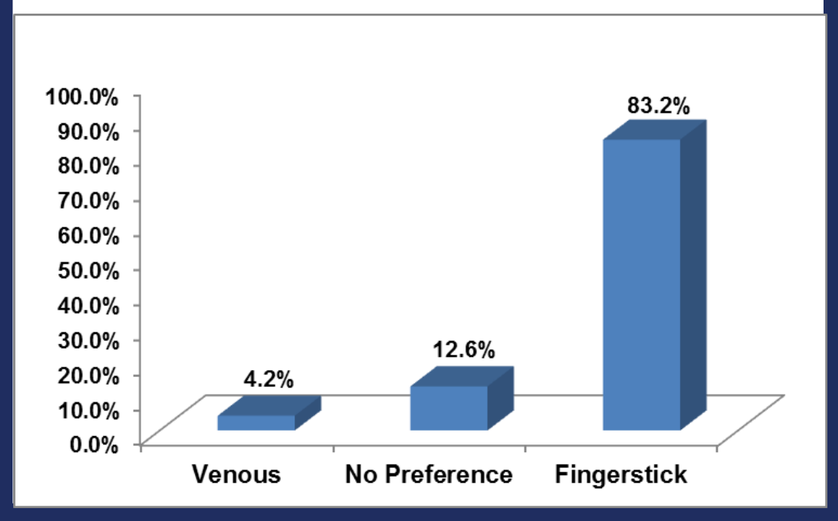


Figure 1: Tac Method Comparison

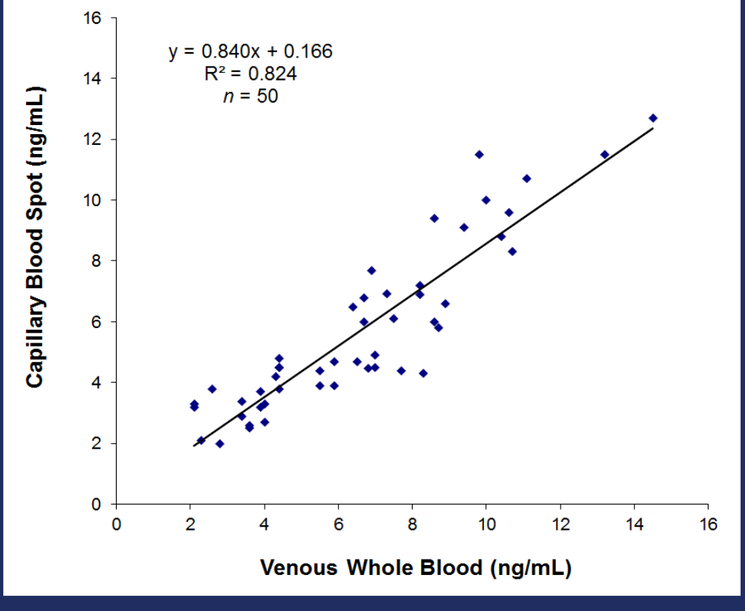
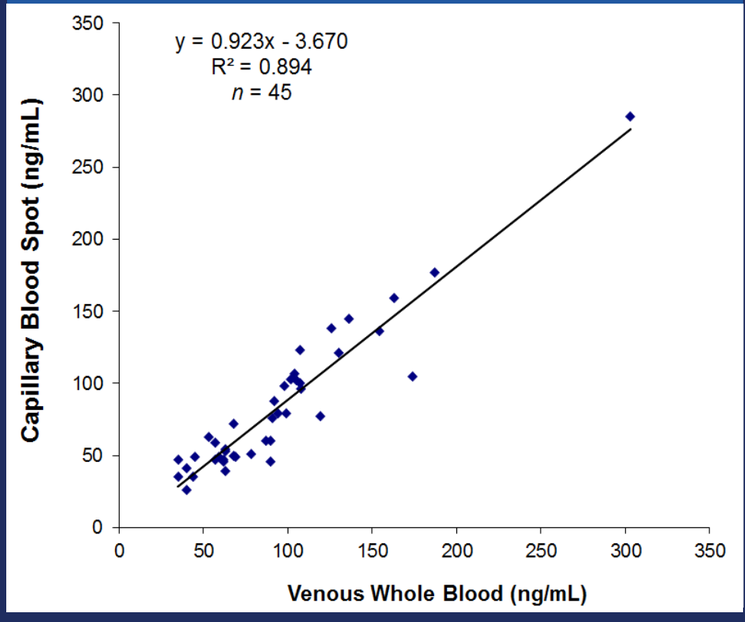


Figure 2: CsA Method Comparison



Conclusions

- Pilot study showed correlation between capillary collected dried blood spots using a Mitra microsampling device compared to venous collected whole blood for both tacrolimus and cyclosporine A.
- Additional optimization strategies to minimize pre-analytical variables (i.e. milking of finger) during the capillary collection process may improve correlation to venous collected samples.
- Overall patient satisfaction was favorable to self-collecting a capillary sample at home vs. going to a phlebotomy collection site in the future.
- The Mitra microsampling device has the ability to collect and use less blood which is especially important for pediatric transplant patients.

References

1. Levine DM, Maine GT, Armbruster DA, Mussell C, Buchholz C, O'Connor G, *et al*. The need for standardization of tacrolimus assays. *Clin Chem*. 2011; **57**(12): 1739-47.