Volumetric Microsampling of Capillary Blood Spot vs Whole Blood Sampling for Therapeutic Drug Monitoring of Tacrolimus and Cyclosporin A: Accuracy and Patient Satisfaction

Article:
Michael M. Mbughuni, et al.
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Guest: Dr. Michael Mbughuni is the director of clinical chemistry and toxicology at the Minneapolis Veteran Affairs Health Care System.

Randye Kaye: Hello and welcome to this edition of JALM Talk, from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

Organ transplant patients require post-transplant therapy with immunosuppressant drugs to prevent organ rejection. The calcineurin inhibitors tacrolimus and cyclosporin A are two examples of drugs commonly used for this purpose. Both tacrolimus and cyclosporin A have narrow therapeutic ranges. In patients who are administered these drugs, drug levels should be monitored by laboratory testing to ensure minimum effective concentrations while avoiding toxic effects. Laboratory-based therapeutic drug monitoring requires patients to come in for blood draws at regular intervals timed relative to drug doses. Patients may need immunosuppressants for the rest of their lives after transplant. Thus, the requirement of drug monitoring can place a significant burden on patients and challenges and access to testing can lower compliance and lead to adverse outcomes.

An original article in the May 2020 issue of JALM explores the use of a microsampling device that could allow for patients to self-collect and ship their blood samples to a laboratory. In this study, volumetric microsampling of capillary blood was validated, and measured tacrolimus and cyclosporin A using tandem mass spectrometry. The first author of this article is Dr. Michael Mbughuni. Dr. Mbughuni is the director of clinical chemistry and toxicology at the Minneapolis Veteran Affairs Health Care System. The study was conducted when Dr. Mbughuni was a clinical chemistry fellow at the Mayo Clinic under the mentorship of senior author Dr. Paul Jannetto. Dr. Mbughuni is our guest for this podcast. Welcome Dr. Mbughuni.

What led you to perform the validation of tacrolimus and cyclosporin A assays from a microsampling device rather than traditional venous blood tubes? What was the significance of this study and were there any surprises?

Michael Mbughuni: All right, we started validation work on the microsampling device because of its ability to collect volumetrically accurate amounts of stable dry blood. This approach opens up the door to improve the burden placed on patients, so, from several toxicology applications such as therapeutic drug monitoring and pharmacokinetic studies where a significant amount of blood for example, 4 mils or more is traditionally collected from the patient. And in our study, we only collect 20 microliters per specimen. So, of significance, this article highlights the ability of the patients to self-collect blood samples for laboratory tests. Transplant patients require a lifelong immunosuppressant therapy which necessitates therapeutic drug monitoring since whole blood drug concentrations are needed to assess compliance and prevent rejection or toxicity.

Patients have to routinely go to a phlebotomy center and have blood drawn. Our study showed home self-collection using capillary dried blood collected with these volumetric microsampling devices could be potentially used to measure two commonly prescribed immunosuppressant drugs, tacrolimus and cyclosporin A. There were indeed a few surprises. The patient satisfaction survey results were very informative about patient's perspective through the entire process. About half of the patients were initially hesitant to perform the capillary finger stick and chose to have assistance. But once they saw how this was done, about 90% of patients stated they would feel comfortable performing the capillary collection themselves next time around. So, overall our patient cohort would prefer to self-collect capillary blood samples for therapeutic drug monitoring at home and in the future, they stated that they found this overall process really to be less painful than traditional venous blood collections.

Randye Kaye: Now your article distinguishes volumetric sampling and non-volumetric sampling. Can you describe that distinction to our audience and explain why volumetric blood spots are advantageous for therapeutic drug monitoring applications?

Michael Mbughuni: Sure. Traditional non-volumetric blood spots are collected onto a flat cellulose blood card containing a marked circumference for the collection. Once the collection reaches the set circumference, a card is allowed to dry before a fixed diameter disc is used to punch a dried blood spot from the card in order to provide volumetric sampling of the specimen.

The problem is research has shown that the volume spotted on the card can vary with the specimen hematocrit resulting in a hematocrit effect which subsequently affects accuracy of the analytical result. So the cards can also have problems with the homogeneity of the surface where the specimen is spotted in addition to challenges in stopping the spotting once the allocated space is filled. For these reasons, traditional

blood cards are associated with key pre-analytical challenges that can affect accuracy and precision of analytical results. Volumetric blood spots are different in that they use capillary action to facilitate spontaneous absorption of a set amount of blood into an absorbed polymetric tip while eliminating the hematocrit bias seen in traditional dried blood spots.

The volume collected is usually 10, 20, or 30 microliters, which is much less than what traditional venous access collects. This is very different from non-absorptive blood spots collected in traditional cellulose cards because a defined amount of blood is collected so that tips cannot be overfilled. The volume collected is not dependent on the specimen hematocrit. So taken together with the capacity to collect a very small amount of sample, the volumetric absorptive microsampling approach overcomes many of the pre-analytical disadvantages associated with traditional blood cards making volumetric microsampling suitable for several toxicology applications such as drug monitoring and pharmacokinetic studies.

Randye Kaye: What are the benefits of using microsampling approach for measuring immunosuppressant drugs from the perspectives of the laboratory, the clinicians, and the patients?

Michael Mbughuni: Sure. In general, therapeutic drug monitoring imposes a lifetime burden on transplant patients because the immunosuppressants are monitored for the rest of their lives to optimize outcomes. Usually venous access is used to collect a significant amount of blood trough or C2 which is the two, our post dose sample for monitoring these calcineurin inhibitors, tacrolimus and cyclosporin A. So it is a timed collection where the patient needs to travel to a phlebotomy site and endure venous access for appropriate monitoring. From a patient and clinician's perspective being able to collect 20 microliters as opposed to 4 mils for therapeutic drug monitoring is a win-win scenario and you have the added benefit that the patient can self-collect from home which should help alleviate the therapeutic drug monitoring burden on the patient, especially if the patient doesn't have to travel for drug monitoring.

For the clinician, the home sampling approach might also be advantageous in that the same laboratory can continue to monitor the patient regardless of their geographic location. Therapeutic drug monitoring more and more is using tandem mass spectrometry to monitor tacrolimus and cyclosporin A. This is becoming the standard of care. Being able to monitor a patient using the same laboratory-developed tests can have advantages for the clinician who doesn't have to worry about analytical differences between methods when the patient relocates to a new location. Lastly, advantages for the laboratory include enhanced specimen stability and less risk

of exposure to pathogens for staff since the specimens are dried and this attenuation deactivates many of the blood-borne pathogens in dried blood spots.

Randye Kaye: Well, can you talk about some of the challenges that you faced in your validation or any other challenges that may generally exist for the use of blood spots in the clinical lab? Are there barriers that prevent this approach from becoming the standard of care?

Michael Mbughuni: Sure. There is a clear work that needs to get done in order to improve analyte recovery from capillary blood spots in comparison to the current methods that extract the compounds from whole blood. So, our study specifically showed analyte recovery from dried capillary samples was a key challenge; however, this is just one hurdle in a long journey that lies ahead. Volumetric microsampling is a relatively new approach that still needs to mature with respect to how robust and reliable the sampling devices are for preparing dried blood spots. Also, more work needs to be done looking at analytical issues that might be associated with home self-collection of volumetric dried blood spots to sort of understand what the pre-analytical issues are when self-collection is done at home and what the untold challenges are when the specimens are collected by a patient and sent to a laboratory for analysis.

So, there might have to be creative studies designed to shed light on this process in order for everyone to gain the confidence needed to implement volumetric dried blood spots as the new standard of care. Some of these studies are already actually starting to emerge, which is a good sign.

Randye Kaye: That's great. Well, finally how may the results of your study advance the broader field of therapeutic drug monitoring? Could your approach be used for other assays?

Michael Mbughuni: Sure. Yes. Our study specifically just compares the volumetric capillary dried blood spot results directly with venous whole blood results, showing that with some reasonable improvement, it is feasible to develop a method that could use either type of specimen for monitoring. It also shows that patients are willing to participate and they think this is a feasible approach. These findings really set the stage for follow-up studies and it also gives many other laboratories a reason to move forward and design their own study which we hope will complement our study by designing an approach that will take a look at more variables than what we focused on in order to move forward with the field. So this approach can be used for many different analytes This is the case, if you search the literature currently, you will find that is growing area of research and researcher is intensifying in many different research groups throughout the world and

many laboratories are incrementally working on the idea of home sampling for toxicology applications using these devices.

Randye Kaye: That's wonderful. Doctor, thank you so much for joining us today.

Michael Mbughuni: Good, thank you very much for having me.

Randye Kaye: That was Dr. Michael Mbughuni from the Minneapolis Veteran Affairs Health Care System describing his JALM original article "Volumetric Microsampling of Capillary Blood Spot vs Whole Blood Sampling for Therapeutic Drug Monitoring of Tacrolimus and Cyclosporin A: Accuracy and Patient Satisfaction." Thanks for tuning in to this episode of "JALM Talk." See you next time and don't forget to submit something for us to talk about.