Self-sampling of blood using a topper and pediatric tubes; a prospective feasibility study for PSA analysis using 120 prostate cancer patients

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Abstract

Objectives: Self-collection of blood for diagnostic purposes by blood collection assist devices (BCAD) has gained a lot of momentum. Nonetheless, there are a lack of studies demonstrating the feasibility and reliability of self-collecting capillary blood for routine (immuno)chemistry testing. In this study we describe the topper technology together with pediatric tubes to enable self-collection of blood and investigated its feasibility for PSA testing by prostate cancer patients.

Methods: 120 prostate cancer patients for which a routine follow-up PSA test was requested, were included in this study. Patients received instruction materials and the blood-collection device consisting of a topper, pediatric tube and base-part, and performed the blood collection procedure themselves. Afterwards a questionnaire was filled-in. Finally, PSA was measured on a Roche Cobas Pro.

Results: The overall self-sampling success rate was 86.7%. Furthermore, when specified per age category, a 94.7% success rate for patients under 70 years and a 25% success rate for patients of 80 years and older was observed. Venous and self-collected PSA were highly comparable when analyzed by Passing–Bablok regression with a slope of 0.99 and intercept of 0.00011, Spearmans correlation coefficient (0.998) and average self-collected PSA recovery of 99.8%.

Conclusions: Evidence is presented that self-collected capillary blood by topper and pediatric tube from the finger is feasible, particularly for patients under 70 years. Furthermore, capillary blood self-sampling did not compromise any of the PSA test results. Future validation in a real-world setting, without supervision and including sample stability and logistics, is required.

Keywords: capillary blood collection; direct to consumer testing; PSA; self-collection

Introduction

At home and self-collection of blood for diagnostic purposes has gained a lot of momentum the last couple of years. The rise of direct-to-consumer companies that offer genetic or alternative diagnostic services has made at home blood collection a standard practice for their services [1–3]. Furthermore, the Covid-19 pandemic triggered a variety of self-collection tools to be routinely used, for diagnosis and monitoring of clinical and wellness indications, including self-testing for Covid-19 [4, 5]. For clinical applications, there is increased interest in the self-collection of blood by patients for many reasons including the avoidance of the venipuncture procedure by a healthcare professional. This avoidance could result in reduced patient time and resources needed for obtaining a blood sample as well as phlebotomy staffing challenges and related costs. For these reasons, several self-collection strategies using different blood collection assist devices (BCAD) have been investigated that include dried blood spots, volumetric absorptive microsampling (VAMS) [6] as well as designed blood collection systems [4, 7–9]. Particularly in the field of drug analysis, such as for therapeutic drug monitoring (TDM), the appropriateness of multiple self-collection systems primarily based on dried blood spots and VAMS has been described and is applied [5, 10]. For the more general chemistry and immunochemistry tests there is however a lack of publications that validate these systems and demonstrate the appropriateness of a self-collection strategy. For many of these tests, the (analytical) performance specifications required for clinical practice can be rather stringent in terms of allowable imprecision and lower limit of quantitation (LLOQ) that pose challenges for the use of alternative systems. Challenges with the systems available…
for self-collection of capillary blood include; (i) uncertainty in sampling volume as associated with dried blood spots, (ii) insufficient sampling volume for routine immunochemistry analyzer systems (VAMS), (iii) sample dilution as is applied for certain devices, (iv) or using whole blood as alternative matrix and hematocrit uncertainty and variation. These procedures add a necessary correction e.g. for sample matrix, volume or dilution that increases the overall test inaccuracy. Furthermore, several other limitations include the inappropriateness of the whole blood matrix, in vitro hemolysis and addition of subcutaneous fluid to sample by the collection procedure. For these reasons alternative methods have been developed using devices that collect capillary blood from skin capillaries of the arm [4]. Direct interfacing with the analyzer and pre-analytical machinery available in the general clinical laboratory is a remaining operational challenge. Most direct to consumer companies that offer routine diagnostic services, therefore use the readily available pediatric tubes and lancets from well-known in vitro diagnostic (IVD) suppliers [11]. Interestingly, these IVD devices are generally only formally certified and approved for use by a health care professional and not for self-collection [12, 13]. Furthermore, thorough validation of these devices for the suitability of self-collection for general clinical chemistry and immunochemistry testing is generally not available in today’s scientific literature or public domain. Only very recently, a first manuscript using the Tasso collection procedures did investigate the use of this system for chemistry measurands [14].

For prostate cancer patients, particularly in the low disease state and often curative setting, PSA testing comprises an essential test to follow-up treatment. Most often this is the only blood test necessary for follow-up and is performed at several follow-up moments in time. Based on this monitoring regimen, the researchers associated with this paper wanted to investigate the feasibility of blood self-collection by prostate cancer patients for PSA analysis. Unfortunately, based on the previous statements, no commercially available systems was considered suitable to enable self-collection of blood by prostate cancer themselves and to enable a PSA test on the routine immunochemistry analyzer present in our laboratory. Therefore a new BCAD device set-up was developed and used, based on compatibility with commercially available pediatric tubes. This resulted in the development of new patented technology that is incorporated into a “topper” device. The topper technology can be added to commercially available pediatric blood collection tubes in order to improve the guidance of the blood originating from the finger into the collection tube. This study describes the development and technology of the topper system. Furthermore, it investigated the feasibility and accuracy of this new technology for PSA testing using self-collected samples from 120 prostate cancer patients.

Materials and methods

Topper technology

The developed topper design and technology is presented as part of the final self-collection device set-up in Figure 1. The topper technology aims to enable an efficient and clean collection of all blood leaving the finger from the puncture side. The design focusses on minimizing the amount of dead volume per blood sample while transferring the sample towards the pediatric collection tube. The topper part (part A in Figure 1) consists of a funnel-based plateau that totally covers and overlaps with a standard pediatric collection tube opening. The funnel guides the applied blood to the funnel center into an integrated capillary. The capillary transfers the blood into the pediatric blood collection tube. To avoid overpressure in the tube, a depressurizing air outlet hole is incorporated in the topper design. These elements are the basis of the technology. In order to have two hands available for the blood collection procedure, thereby enabling guidance of finger blood to the puncture side by using the second hand, a generic base-part (Figure 1, part C) was added that enabled the device to have a stable standing. The produced topper was initially developed using 3D-printed prototyping and the final part used in the feasibility study was produced using injection molding. The used topper part is not CE certified nor commercially available. The presented intellectual property of the topper technology is part of the original patent NL2019/079641. For the PSA study, the pediatric 300 µL Microvette serum tube from Sarstedt (Sarstedt Cat No. 20.1308.100) was used for blood collection (Figure 1, part B).

Study population and inclusion

In the prospective cohort study a total of 120 patients, for which a PSA test was requested for routine clinical care in the Netherlands Cancer
Institute between June and December 2022, were included. Inclusion was performed by asking routine clinical follow-up patients for which a PSA analysis was scheduled to participate. After consent was obtained, one additional SST (BD) tube was added to the blood collection order and the scheduled venipuncture for blood collection was performed. Thereafter, patients were guided to a separate location to perform the self-collection procedure. Informed written consent was obtained from all participants. The study as in accordance with the World Medical Association Declaration of Helsinki regarding ethical conduct of research in involving human subjects and was approved by the local Medical Ethical Committee (MEC) (NL number NL76225.031.20).

Self-collection of blood sample

All participants received instruction materials by poster as well as video. Thereafter they were asked to perform the blood collection procedure according to the instructions, that were given in the Dutch language (Supplementary Data 1). These included the next preparation steps: (i) self-assembling of the collection device, (ii) cleaning the hand using an alcohol swab, (iii) heating of the hand and finger by using a cup of hot water (1:1 boiled water/tap water) for 2 min, (iv) holding the hand next to the body for 1 min. Thereafter the finger was punctured using a lancet (BD blue Cat No. 366594) and blood from the finger was collected by the collection device (see Figure 1). All blood, including the first drop, was collected and participants were allowed to push the finger to guide the blood flow to the finger puncture site.

Observation of self-collection procedure

Executive researchers observed the self-blood collection procedure by using an observation list that included recording the time and duration of the different procedure-steps, the correctness of the different procedure steps, and any other observation considered relevant. When considered relevant, they could additionally instruct the patient to make sure the procedure was performed according to the instructions. Finally, the participant was asked to fill in a questionnaire regarding their satisfaction with the blood collection procedure and device.

PSA and sample hemolysis

The collected SST tubes were spun down (10 min, 2500 g at room temperature (RT)) and the serum Microvette tubes were spun (10 min, 1700 g, RT). Next, the Microvette was slid into an adapter tube and both the SST tube and Microvette tube were analyzed for Hemolysis-Index (HI) as well as PSA on a Roche Cobas Pro system. The LLOQ applied for PSA was 0.01 μg/L and assay imprecision was ≤2.0%. Although the HI is dimensionless, in our set-up 1 HI unit corresponds to a hemoglobin concentration of approximately 1 mg/dL.

For comparison of venous PSA with self-collected PSA Passing-Bablok regression analysis was performed and Spearman correlation coefficients were calculated (Analyse-it 3.92). Requirements for acceptable agreement as stated in the MEC approved protocol were: Spearman correlation coefficient >0.9 and 95% confidence interval of slope includes 1.0 or is within total desirable bias criterion of 10.6% based on the biological variation from the from the EFLM biological variation database [15]. Furthermore, the self-collected PSA recovery of all individual samples was calculated.

Results

Feasibility of self-collection procedure

In 104 of the 120 cases a blood sample was collected which contained sufficient serum for PSA analysis, thereby resulting in an overall success rate of 86.7%. Additional analysis indicated that there was a relationship between the success rate and patient age (Table 1). For patients under 60 years (n=19) a 100% success rate and patients under 70 (n=57) a 94.7% success rate was observed.

Two patients under 70 years were unable to collect a blood samples due to (i) a suspected mild intellectual disability of a patient thereby not able to accurately follow the instructions and (ii) a patient with many warts and calluses on his fingers complicating the puncturing and blood flow from the finger. All other (n=12) failed self-collection procedures were caused by limited blood flow from the finger, resulting in limited to none blood collection.

Since it was noted that the observed temperature of the finger at the time of the blood collection might affected the blood flow and thereby success rate, after the first 18 patients both the wrist as well as the finger temperatures were measured using Medisana TM A77 infrared body thermometer. The average temperature of the patients with and without a successfully collected sample were 36.0°C and 36.1°C for the wrist and 35.9 and 35.7°C for the finger, respectively. Furthermore, for the wrist 10% was below the thermometer LLOQ (<34.0°C) for both patient groups. For 56% of the patients with a successful blood collection and 60% of the patients without a successful blood collection the finger temperature was below the thermometer LLOQ.

Furthermore, 19% of the patients with a successful sample collection and 27% of the patients without a successful sample collection used anticoagulants.

Table 1: Finger blood collection success rate specified per age category. n represents the number of study participants within the age category. And % success represented the % of patients that were able to self-collect a blood sample that resulted in sufficient serum for PSA analysis.

<table>
<thead>
<tr>
<th>Age, years</th>
<th>n</th>
<th>% success</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>2</td>
<td>100.0 %</td>
</tr>
<tr>
<td>50–54</td>
<td>6</td>
<td>100.0 %</td>
</tr>
<tr>
<td>55–59</td>
<td>11</td>
<td>100.0 %</td>
</tr>
<tr>
<td>60–64</td>
<td>14</td>
<td>85.7 %</td>
</tr>
<tr>
<td>65–69</td>
<td>24</td>
<td>95.8 %</td>
</tr>
<tr>
<td>70–74</td>
<td>32</td>
<td>84.4 %</td>
</tr>
<tr>
<td>75–79</td>
<td>27</td>
<td>81.5 %</td>
</tr>
<tr>
<td>≥80</td>
<td>4</td>
<td>25.0 %</td>
</tr>
</tbody>
</table>
PSA method comparison

The observed PSA concentrations ranged from <0.01 μg/L to 1827 μg/L. The PSA results from the venous sample and self-collected sample were compared using Passing–Bablok regression and the obtained slope was 0.99 (95% CI: 0.98–1.00) and intercept was 0.00011 (95% CI: 0.000041–0.00022), see Figure 2. The observed Spearman’s correlation coefficient was 0.998 (95% CI: 0.997–0.999). Furthermore, the observed PSA differences between the self-collected sample and venous sample are presented in a Bland-Altman plot in Figure 3. The average recovery was 99.8% and ranged from 78.7 to 150%. For the one patient with a 150% recovery the observed venous PSA was 0.0114 μg/L and self-collected PSA was 0.0171 μg/L. Because of the large relative difference between these two samples, samples were rerun for PSA re-analysis about 3 weeks later, including a freeze-thaw cycle. Venous and self-collected PSA were 0.0106 μg/L and 0.0110 μg/L respectively.

Patient questionnaire

After performing the self-collection, all patients received a questionnaire with questions regarding the self-collection procedure and device. The questions could be answered by quantitative 1 (agree) to 5 (disagree). The results are presented in Figure 4.

Hemolysis

The median HI value for the venous collected sample was 6 (range 0–94) and for the self-collected sample from the finger 10.5 (range 0–495). The difference between the venous and self-collected sample, tested by paired t-test was significant p=0.0014. To investigate the potential impact for the observed increased hemolysis, the % of accepted samples for measurands sensitive for in vitro hemolysis as used by our laboratory is presented in Table 2. The HI cut-offs included in the table are based on self-validated HI and includes the correction procedures as applied at the Netherlands Cancer Institute. For the latter the HI limit represents the upper limit of the HI range that was previously validated to allow for accurate correction for HI [16, 17].

Discussion

This study describes the procedure and topper technology used for self-collection of capillary blood from the finger and presents a feasibility study thereof for PSA analysis in prostate cancer patients. The topper technology was designed in order to enable collection of 300 μL of blood by patients themselves and to enable easy adaption onto the analyzer systems available at routine clinical laboratories. Within the studied population, an overall success rate of 86.7% was achieved, with age as possible prognosticator for...
a successful self-collection procedure. Particularly for patients under 70 years, self-collection from the finger resulted in a high success rate (95%). Furthermore, the PSA results from self-collected samples were all highly comparable to the PSA results obtained from venous blood sampling.

Self-collection of blood samples using BCAD for diagnostic purposes has gained a lot of interest, particularly in the direct-to-consumer testing area. It provides a strategy for clinical settings to avoid patient visits to phlebotomy departments and related costs, staffing requirements and other associated resources. Most studies have investigated self-collection solutions for TDM and infectious disease testing [4, 10]. Unfortunately, no recent evidence for general chemistry and immunochemistry testing including tumor markers is publically available that the authors know of,

Figure 3: Bland–Altman plot. Difference between self-collected and venous PSA were expressed relative to venous PSA concentration. LoA, level of agreement.

Figure 4: Patients answers to the questions.
although many offer diagnostic services based on self-collected capillary blood [11, 18, 19]. Demonstration of the appropriateness of alternative collection approaches is of the utmost importance to ensure accurate and reliable test results suitable for clinical management. This research is the first prospective trial that investigated the feasibility of self-collecting a capillary blood sample from the finger, using routinely available pediatric blood collection tubes for PSA analysis in prostate cancer patients. The procedure, in which the topper technology was added to simplify the collection for patients themselves, was otherwise designed to use commercially available components (pediatric tubes and lancets), and to interface with the hardware available on laboratories by avoiding unnecessary sample management steps. Other strategies have focused either primarily on the blood collection phase [20], stability preservation by introducing a stabilizer and thereby sample dilution [7, 9], or using micro-volumes not suitable for the routine clinical analyzer systems [10].

The first part of the study focused on enabling the self-collection of a suitable blood sample. It was found that the patient age was a major discriminator of the success rate. Particularly patients younger than 70 years were successful in collecting a suitable sample (95 %). Although based on a very low number of (n=4), our results indicate that patients of 80 years and older might not be an appropriate group to offer blood self-collection services by a topper, as they were rarely capable to self-collect a sample (25 %). To our knowledge, this is the first description of the relevance of age for the self-blood collection success-rate. The below 70 years group also included individuals with valid reasons for failing the self-collection procedure including the presence of many warts and calluses on the fingers and suspected mild intellectual disability thereby having great difficulties following the instructions. Another observed challenge was the lack of an appropriate Dutch language level by participants to understand the instruction materials provided in Dutch. The most relevant cause of a failed self-collection procedure was the lack of sufficient blood flowing out of the finger. The standard heating of the hand prior to the self-collection as part of the procedure, the use of anticoagulants by some participants, and forcing the blood to the puncture site, were not sufficient to ensure adequate blood flow from the finger. This is acknowledged by the patients in the questionnaires with respect to obtaining enough blood from the finger as the most challenging step in the procedure. Also, the collection procedure did not discard the first drop of blood from the finger and allowed for a second hand to push the finger to guide the blood to the puncture site. Based on the obtained PSA results, these procedures did not compromise the suitability of the sample for PSA analysis.

When the PSA results were compared, a high correlation (0.998) and regression slope of 0.99 with a regression intercept close to zero, and significantly lower than the LLOQ, were observed that indicate equality of the venous and self-collected sample. Furthermore, the average recovery was 99.6 % and ranged from 78.7 to 150 %. The high 150 % recovery point that also jumps out in Figure 3 was observed at the very low end of the analytical range and would, by rounding as part of our standard reporting in our laboratory, result in a 0.01 µg/L for the venous sample and 0.02 µg/L for the self-collected sample. In this measurement range, the large relative difference therefore only represented a minor absolute difference in PSA concentration, differed only 1 reporting unit.

Alternative approaches for decentralized PSA testing have also been described that include point of care systems such as the PSAwatch a point of care system that has reported measurement range of 0.1–25 µg/L and inferior accuracy [21] and the CancerCheck PSA test on a Concile 100 reader that also lacked appropriate correlations with serum-based reference measurement systems but was considered appropriate for screening purposes [22]. Alternative approaches for centralized PSA analysis include the Biosafe collection device connected to a modified version of the Hybritech PSA assay that required some additional sample preparation steps [8]. Also, dried blood-spot based assays primarily designed for prostate cancer screening purposes have been investigated [23, 24]. However, these would generally require extraction and dilution and therefore potentially compromise the PSA accuracy and LLOQ by addition of dilution step and correction therefore, and measurement at the low(er) analytical measurement range.

<table>
<thead>
<tr>
<th>Hemolysis cut-off (± in mg/dL)</th>
<th>Venous sample, %</th>
<th>Self-collected sample, %</th>
</tr>
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<tbody>
<tr>
<td>&lt;15, NSE</td>
<td>92 %</td>
<td>61 %</td>
</tr>
<tr>
<td>&lt;16, LDH</td>
<td>92 %</td>
<td>62 %</td>
</tr>
<tr>
<td>&lt;18, K</td>
<td>95 %</td>
<td>64 %</td>
</tr>
<tr>
<td>&lt;20, AST</td>
<td>96 %</td>
<td>64 %</td>
</tr>
<tr>
<td>&lt;40 (allow LDH correction)</td>
<td>98 %</td>
<td>86 %</td>
</tr>
<tr>
<td>&lt;73 (allow AST correction)</td>
<td>99 %</td>
<td>90 %</td>
</tr>
<tr>
<td>&lt;91 (allow K correction)</td>
<td>99 %</td>
<td>94 %</td>
</tr>
<tr>
<td>&lt;155 (sodium &amp; chloride)</td>
<td>100 %</td>
<td>96 %</td>
</tr>
</tbody>
</table>

NSE, neuron-specific enolase; LDH, lactate dehydrogenase; K, potassium; AST, aspartate aminotransferase.
Although, it is demonstrated that highly comparable PSA results are obtained for the venous and self-collected blood samples and the venous sampling for PSA analysis seems to be replaceable by the self-collection procedure, some limitations need to be addressed. First, this study deliberately did not include sample PSA stability, unsupervised collection and logistic issues that would be part of a truly at-home collected sample. The reason was that this study focused solely on the appropriateness of the developed self-collection technology and procedure and therefore no other potential confounders that could bias this observation, were allowed in this study. In this way, any and all variation between results could be directly attributed to the self-collection procedure and uncertainty associated with the standard venous sample procedure. The effect of supervision and the ability to ask questions to the researchers during the collection procedure, might have affected the success rate in a positive manner. The appropriateness of the topper technology for self-collection of blood in a at-home setting, without supervision and including sample logistics and stability, therefore requires additional validation in a consecutive validation study. Others have demonstrated PSA whole blood stability for up to 48 h that should enable such a procedure [25]. However, an extended PSA stability over 48 h might be required to ensure sufficient PSA stability to support all sorts of logistic solutions, and should therefore be validated. Another relevant observation was the significant higher in vitro hemolysis present in the self-collected capillary samples when compared to the venous samples. PSA is rather insensitive to in vitro hemolysis; HI cut-off applied for PSA is 2,200, and was not affected by the observed increased in vitro hemolysis present in the self-collected samples. To have an estimate of the appropriateness of the self-collected capillary samples for analyzing measurands known to be sensitive for in vitro hemolysis, the impact of the measured HI on the reporting of these measurands was included in the analysis. Here, for the measurements most sensitive (NSE and LDH) only about 60 % of the self-collected samples would have been accepted. Although for LDH this might be increased to 86 %, still a significant number of samples would be unsuitable. Others that used the Tasso system also reported significant in vitro hemolysis in the capillary samples when compared to the venous sampling [14]. This suggest that the self-collection of capillary blood might not be an interesting alternative for measurands sensitive to in vitro hemolysis.

In conclusion, a collection procedure and new topper technology assisted approach is presented to enable self-collection of blood particularly for patients below 70 years. Furthermore, although it is demonstrated that the self-collected sample does not compromise the accuracy of PSA, a future real-world study is required to demonstrate and validate its true clinical potential.

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Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: NvdB, SF and HvR have stock or stock options of Self Safe Sure Blood collection B.V., NvdB and HvR are inventors on pateent (NL2019/079641).

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The study was approved by the local Medical Ethical Committee (NL number NL76225.031.20).

References


Supplementary Material: This article contains supplementary material (https://doi.org/10.1515/cclm-2023-0272).