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Hematocrit Determination using a Volumetric Absorptive Microsampling Technique in Patients with Pancreatic Cancer

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ABSTRACT

Background: Hematocrit is usually measured from venous blood collected by invasive venipuncture. This study was performed to determine hematocrit accurately and precisely using minimally invasive volumetric absorptive microsampling (VAMS) technique. Such technique is to be applied to determining hematocrit in various clinical settings for the care, including therapeutic drug monitoring, of neonatal or epileptic patients, or patients with high risk of infection or bleeding. **Methods:** The study was performed using 31 VAMS samples obtained from 21 pancreatic cancer patients. Hematocrit was determined using the values of potassium concentrations obtained from blood in VAMS tips (Hct_{VAMS}). Hct_{VAMS} was compared with hematocrit measured from blood collected by venipuncture (Hct_{VP}). The accuracy and precision of Hct_{VAMS} in comparison to Hct_{VP} were evaluated using Bland-Altman plot, Deming regression and mountain plot. **Results:** Bland-Altman plot displayed a random scattering pattern of the differences between Hct_{VAMS} and Hct_{VP} with the mean bias of –0.010 and the 95% limit of agreement ranging from –0.063 to 0.044. Deming regression for Hct_{VAMS} and Hct_{VP} line demonstrated very small proportional and constant biases of 1.04 and –0.003, respectively. Mountain plot exhibited a narrow and symmetrical distribution of the differences with their median of –0.011 and central 95% range from –0.049 to 0.033. **Conclusion:** Hematocrit was accurately and precisely determined using less invasive VAMS technique. Such technique appears to be applicable to determining hematocrit in situations that venipuncture is not favorable or possible.

KEYWORDS: Hematocrit determination, pancreatic cancer, potassium concentration, venous blood sampling, volumetric absorptive microsampling

Hematocrit, the volume percentage of erythrocytes in whole blood, is an essential hematological parameter used for identifying various clinical conditions such as anemia and erythrocytosis, and monitoring the clinical effects of a drug therapy in patient care and research.[1)] Hematocrit is usually measured from a large volume of venous blood collected by venipuncture that is invasive, and requires a phlebotomist and the visit to healthcare facilities. In circumstances in which venous blood sampling is not favorable or possible, hematocrit needs to be measured using an alternative approach.

Volumetric absorptive microsampling (VAMS) approach has been used increasingly in recent studies as an alternative to venipuncture for obtaining blood samples.[2-7)] VAMS is a technique that absorbs a small fixed volume of blood from a

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patient's fingertip onto a hydrophilic polymer tip and, therefore, is minimally invasive, less painful and not requiring a phlebotomist compared with the blood sampling by venipuncture.[8,9] Hence VAMS is more practical than venous blood sampling in situations that venipuncture is not favorable or possible including but not being limited to the measurement of drug concentrations and hematocrit values from neonatal or epileptic patients, or patients with high risk of infection or bleeding.[9,10]

The determination of hematocrit is necessary in therapeutic drug monitoring especially when whole blood concentration (C_b) needs to be converted to plasma concentration (C_p), for example, on comparing measured C_b with the recommended reference ranges of C_p.[11,12] While C_p is mostly used in deriving pharmacokinetic parameters,[13,14] only C_b is measurable in VAMS samples when collected from the fingertips of patients. The conversion of C_b into C_p depends on the patient's hematocrit, as hematocrit influences the blood-to-plasma concentration ratio of a drug.[11,12,15] Hence, the C_p of a drug can be determined from hematocrit and the C_b measured simultaneously using VAMS technique without a separate venipuncture.

Potassium concentrations are strongly linked to the number of erythrocytes in blood.[11,16] In humans, approximately 98% of potassium is located inside the cells.[17] The potassium concentrations in erythrocytes in the range of 100-105 mEq/L are 20 to 30 times higher than those in serum in the range of 3.5-5 mEq/L.[18,19] Since erythrocytes constitute approximately 99% of human blood cells, the potassium concentrations in erythrocytes are the main contributor to those in whole blood.[16,20] Hence, hematocrit can be determined from the potassium concentrations measured in VAMS tips.[11,16]

A method that determines hematocrit from potassium concentrations using VAMS technique was previously developed by soaking VAMS tips into precollected blood in laboratory settings.[11] This study was performed to evaluate whether such method is applicable to the clinical settings using VAMS samples that were obtained directly from the fingertips of patients. More specifically, this study was conducted in pancreatic cancer patients to determine whether such VAMS technique is safe enough to apply to the patients with high risk of infection and bleeding.

Methods

Study participants and blood sample collection

This study was conducted in patients with pancreatic cancer who were receiving the combination therapy of nab-paclitaxel and gemcitabine at Seoul National University Hospital, Seoul, Republic of Korea. All participants signed a written informed consent form after having been explained the objective of the study and its procedures. This study was approved by the Institutional Review Board (IRB) of the hospital (IRB number, H-2103-093-1205) and conducted in compliance with the Declaration of Helsinki. Blood samples were obtained by placing VAMS tips (Mitra 20 μL; Neoteryx, Torrance, CA, USA) after pricking the participant's finger to bleed. The samples were collected during the intravenous infusion of nab-paclitaxel on the first day of each four-week cycle of chemotherapy. The samples were stored at −70°C in an aluminum foil bag with a desiccant until the potassium concentrations were measured.

Potassium extraction and concentration measurement

After thawing at room temperature, a VAMS tip was placed in a microtube. For potassium extraction, the tube was shaken for 30 minutes at 35°C in a shaking incubator at the rotation speed of 1,200 rpm after adding a 460-μL aqueous solution containing potassium chloride at a concentration of 1.6 mEq/L. Potassium concentration was measured from a 300-μL aliquot of the aqueous extract placed in a vial using a chemistry analyzer (BA 400; BioSystems S.A., Barcelona, Spain) equipped with an ion-selective electrode module (Medica, Bedford, MA, USA). The measured value of potassium concentration was adjusted by subtracting the average value of potassium concentrations obtained from three blank VAMS tips that were prepared without absorbing blood for the determination of the baseline values.

Statistical Analysis

Hematocrit (Hct_{VAMS}) was determined from the adjusted potassium concentration using the linear regression formula; $Hct_{VAMS}=0.187\times$potassium concentration-0.028.[11] Hct_{VAMS} was compared with hematocrit (Hct_{VP}) measured on the same day of the study by the clinical chemistry laboratory of the

hospital. Hct_{VP} was measured using an automated hematology analyzer (Sysmex XE-2100; Sysmex, Kobe, Japan) from venous blood samples collected in EDTA tubes.

A Bland-Altman plot was used to evaluate the accuracy and precision of Hct_{VAMS} in comparison to Hct_{VP} by computing the mean bias and the 95% limit of agreement (LoA), respectively.[21-23] A mean bias close to 0 indicates that the determination of hematocrit was accurate, while a narrow range of 95% LoA does that the determination was precise.[24] A Deming regression was used to evaluate the proportional and constant biases in the agreement between Hct_{VAMS} and Hct_{VP}. The slope of regression line close to 1 means that the proportional bias was small, while the intercept close to 0 does that the constant bias was also small.[24] A mountain plot was used to evaluate the central tendency and variance of the differences between Hct_{VAMS} and Hct_{VP}. The values of Hct_{VAMS} subtracted by Hct_{VP} were sorted and assigned cumulative percentiles in order of magnitude.[25] The percentiles were drawn against the differences, from which the median and central 95% range of the differences were obtained.[25] The median difference (i.e., central tendency) close to 0 indicates that the determination of hematocrit was accurate, while the narrow central 95% range (i.e., variance) does that the determination was precise. All statistical analyses were performed using GraphPad Prism version 9.5.1 (GraphPad Software, San Diego, CA, USA) or MedCalc Statistical Software version 20.305 (MedCalc Software Ltd, Ostend, Belgium).

Results

Participant characteristics

A total of 21 participants were recruited in this study. The participants consisted of twelve males (57%) and nine females (43%) whose median age was 63 years old ranging from 48 to 79 years old (Table 1). Fourteen participants (67%) provided one (one cycle of gemcitabine/nab-paclitaxel administration), five participants (24%) two (two cycles), one participant (5%) three (three cycles), and one participant (5%) four evaluable samples of VAMS (four cycles). Hence, a total of 31 VAMS samples were included in the analysis.

Table 1. Participant characteristics

	Total (n = 21)
Sex, n (%)	
Male	12 (57)
Female	9 (43)
Age (years)	
Mean±SD	62.6±7.94
Median (range)	63 (48-79)
Number of VAMS samples per participant, n (%)	
One sample	14 (67)
Two samples	5 (24)
Three samples	1 (5)
Four samples	1 (5)
Hct_{VAMS}	
Mean±SD	0.343±0.046
Median (range)	0.343 (0.243-0.433)
Hct_{VP}	
Mean±SD	0.353±0.048
Median (range)	0.350 (0.248-0.458)

SD, standard deviation; VAMS, volumetric absorptive microsampling; Hct_{VAMS}, hematocrit determined from the potassium concentrations measured in blood collected using volumetric absorptive microsampling technique; Hct_{VP}, hematocrit measured in blood collected by venipuncture

Measurement of potassium concentrations

Potassium concentrations were measured in 2 separate batches (n=18 and 13). In blank VAMS samples, the mean±standard deviation (SD) concentrations were 1.40±0.01 and 1.53±0.02 mEq/L in the first and second batches, respectively. In the VAMS samples collected from study participants, the mean±SD concentrations were 3.46±0.21 mEq/L ranging from 3.07 to 3.86 mEq/L and 3.39±0.23 mEq/L ranging from 2.98 to 3.89 mEq/L in the first and second batches, respectively. The mean±SD concentrations adjusted by the blank measurements were 2.07±0.21 mEq/L ranging from 1.67 to 2.46 mEq/L and 1.86±0.23 mEq/L ranging from 1.45 to 2.36 mEq/L in the first and second batches, respectively. When combined the two batches, the mean±SD concentrations were 1.98±0.25 mEq/L ranging from 1.45 to 2.46 mEq/L.

Statistical Analysis

Hct_{VAMS} ranged from 0.243 to 0.433 with the mean±SD of 0.343±0.046, while Hct_{VP} did from 0.248 to 0.458 with the mean±SD of 0.353±0.048 (Table 1, Fig. 1). A Bland-Altman plot displayed a random scattering pattern of the differences between Hct_{VAMS} and Hct_{VP} with the mean bias (i.e.,

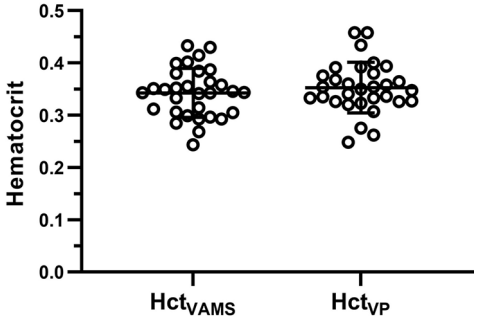

Fig. 1. Dot plot of Hct_{VAMS} and Hct_{VP} with the mean and standard deviation (Hct_{VAMS}, hematocrit determined from the potassium concentrations measured in blood collected using volumetric absorptive microsampling technique; Hct_{VP}, hematocrit measured in blood collected by venipuncture)

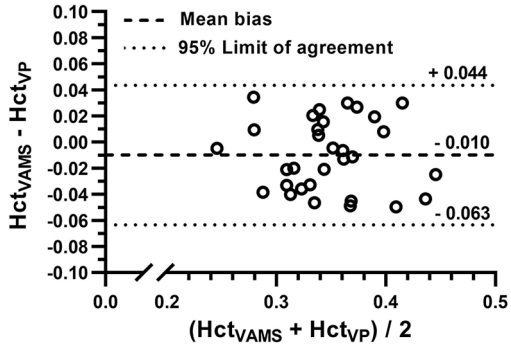

Fig. 2. Bland-Altman plot of the differences between Hct_{VAMS} and Hct_{VP} (Hct_{VAMS}, hematocrit determined from the potassium concentrations measured in blood collected using volumetric absorptive microsampling technique; Hct_{VP}, hematocrit measured in blood collected by venipuncture)

accuracy) of –0.010 and the 95% LoA (i.e., precision) ranging from –0.063 to 0.044 (Fig. 2). A Deming regression demonstrated very small proportional and constant biases between Hct_{VAMS} and Hct_{VP} with the slope of 1.04 (95% confidence interval [CI], 0.77 to 1.31) and the intercept of –0.003 (–0.094 to 0.088), respectively (Fig. 3). A mountain plot showed an approximately symmetrical distribution of the differences between Hct_{VAMS} and Hct_{VP} with their median of –0.011 and central 95% range from –0.049 to 0.033 (Fig. 4).

Discussion

In this article, we present the results of the study that explored an approach of hematocrit determination from potassium concentrations measured in the VAMS samples

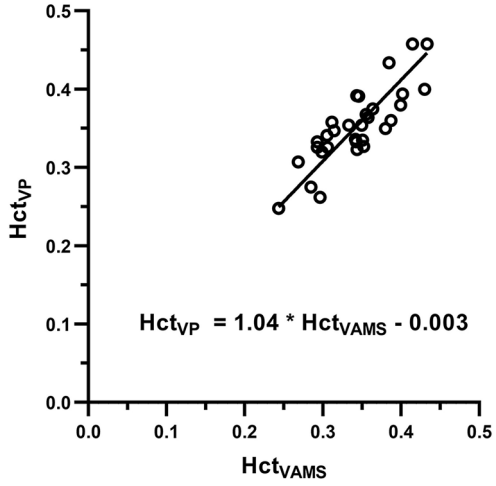

Fig. 3. Deming regression between Hct_{VAMS} and Hct_{VP} (Hct_{VAMS}, hematocrit determined from the potassium concentrations measured in blood collected using volumetric absorptive microsampling technique; Hct_{VP}, hematocrit measured in blood collected by venipuncture)

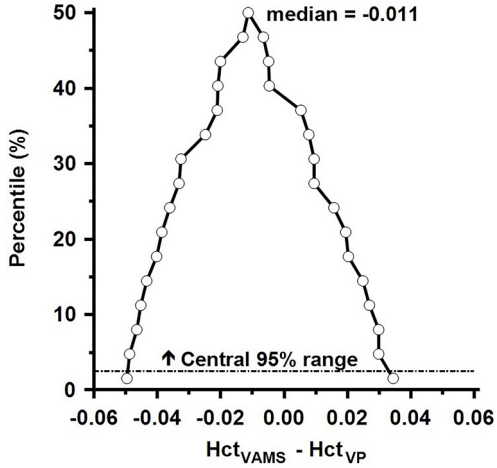

Fig. 4. Mountain plot of the differences between Hct_{VAMS} and Hct_{VP} (Hct_{VAMS}, hematocrit determined from the potassium concentrations measured in blood collected using volumetric absorptive microsampling technique; Hct_{VP}, hematocrit measured in blood collected by venipuncture)

obtained from patients with pancreatic cancer. The results demonstrated that the determination was accurate and precise as evaluated using a Bland-Altman plot, a Deming regression and a mountain plot. Hence, such an approach is applicable to the clinical settings, covering a hematocrit range of 0.248 to 0.458, where hematocrit needs to be measured from VAMS samples that were collected from the fingertips of patients instead of invasive venipuncture. This approach is also useful

in therapeutic drug monitoring where C_b measured in a VAMS sample needs to be converted to C_p.[11,12]

Capiau *et al.* determined hematocrit from potassium concentrations measured in 56 VAMS tips soaked in preocollected venous blood and compared with hematocrit measured in the corresponding venous blood.[11] In a validation of the determination method, a Bland-Altman plot displayed the mean bias of 0.004 and the 95% LoA ranging from −0.043 to 0.051.[11] In another study by Capiau *et al.*,[16] hematocrit was determined from potassium concentrations in the 111 dried blood spot (DBS) samples that were prepared by dropping precollected venous blood on. A Deming regression demonstrated a line with the slope of 0.94 (95% CI, 0.86 to 1.02) and the intercept of 0.019 (−0.004 to 0.042) after adjusted for the mean bias of −0.019 between the determined and measured values that was derived from a Bland-Altman plot.[16]

In this study, the hematocrit determined from the 31 VAMS samples that were collected from the fingertips of patients with pancreatic cancer demonstrated a good agreement with those measured from the venous blood samples of the same patients. Compared with the results of Capiau *et al.*,[11] a Bland-Altman plot exhibited a slightly lower degree of accuracy and precision, because of the smaller sample size, with the mean bias of −0.010 and 95% LoA ranging from −0.063 to 0.044, respectively (Fig. 2). In comparing with the results of the DBS study by Capiau *et al.*,[16] a Deming regression demonstrated the comparable proportional and constant biases with the slope of 1.04 (95% CI, 0.77 to 1.31) and the intercept of −0.003 (−0.094 to 0.088), respectively (Fig. 3). The smaller sample size might also have contributed to the slightly wider 95% CI of the slope and intercept. Complementary to the Bland-Altman plot and the Deming regression, a mountain plot displayed a narrow and symmetrical distribution (central 95% range, −0.049 to 0.033) of the differences between Hct_{VAMS} and Hct_{VP}, which was centered at −0.011 (Fig. 4). Overall, considering that the VAMS samples were collected from real patients under a complicated clinical environment, the hematocrit determination method using VAMS technique is applicable to the most clinical settings in which venipuncture is not favorable or possible.

VAMS would be a practical alternative to venipuncture in determining hematocrit in a wide variety of circumstances. VAMS is less invasive, less painful compared with venipuncture.[4] VAMS collects a very small volume of blood from the fingertips of patients, while venipuncture does a large volume of venous blood from the arm vein of patients.[10] VAMS is particularly well-suited for patients who are at risk of infection or bleeding, such as those immunocompromised or taking anticoagulants.[10] VAMS is also a good option for patients who are reluctant to undergo venipuncture, such as neonates, those with epilepsy and those with difficult venous access.[9,26] Furthermore, VAMS samples can be collected by patients themselves or their family members and sent to a laboratory under ambient conditions.[27-29] VAMS technique, therefore, enables remote hematocrit monitoring without visiting healthcare facility, which can be especially burdensome for the elderly and the neonates.[9,30]

The determination of hematocrit by measuring potassium concentrations appears to be useful in various research settings such as clinical pharmacokinetic studies using VAMS technique in which C_b needs to be converted to C_p.[11] The C_b measured in a VAMS sample is convertible to C_p by using the corresponding hematocrit value because the blood-to-plasma concentration ratio (i.e., C_b/C_p) of a drug depends on hematocrit.[2,11,12,15,27] For example, the unmeasured C_p of radotinib was determined from C_b measured in DBS samples and hematocrit from venous blood using a formula; C_p of radotinib=C_b of radotinib/(1−hematocrit+[hematocrit]^2).[15] Similarly, the unmeasured C_p of tranexamic acid was derived from C_b measured in VAMS samples and hematocrit from additional venipuncture using a formula; C_p of tranexamic acid=C_b of tranexamic acid/(1−hematocrit).[31] Incidentally, the determination method in this study is a simultaneous blood sampling approach that can be used for determining C_p by measuring C_b and hematocrit from the same VAMS collection without a separate venipuncture.

There are some limitations in this study. The sample size was relatively small (n=31), which is below the recommended sample size of at least 40 in comparing two measurement procedures based on the guideline from the Clinical and Laboratory Standards Institute.[22] It was challenging to recruit patients with pancreatic cancer who were willing to participate in VAMS sample collection. Despite the small sample size, the determination of hematocrit was accurate (mean bias between Hct_{VAMS} and Hct_{VP}, −0.010) and precise (95% LoA, −0.063 to 0.044; Fig. 2). In the Bland-Altman plot, observed was a slightly negative bias of −0.010 between Hct_{VAMS} and Hct_{VP}. This bias may be associated with the time lag in the range of two to eight hours between venipuncture for direct hematocrit

measurement and VAMS sample collection. Even this study was conducted in a complex clinical setting, the bias was not markedly different from the mean bias of 0.004 reported in a study using the VAMS samples prepared from precollected venous blood.[11] The other limitation is that the determination covers only hematocrit ranging from 0.248 to 0.458 because the study population was cancer patients whose hematocrit values tend to be low.[32-34] Further study is warranted to assess the accuracy and precision of determination in a population with a higher range of hematocrit.

Conclusion

This is the first study that determined hematocrit by measuring potassium concentrations from a very small volume of blood collected using VAMS samples obtained directly from the fingertips of patients. The determined hematocrit was accurate and precise with small proportional and constant biases as compared with hematocrit measured from a large volume of venous blood collected by invasive venipuncture. The VAMS technique was acceptable for the pancreatic cancer patients with the high risk of infection and bleeding. Such technique is applicable to determining hematocrit in a wide variety of circumstances that venipuncture is not favorable or possible, using less invasive, less painful and less cumbersome VAMS technique in place of more penetrating, more hurtful and more inconvenient venous blood sampling.

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Conflicts of Interest

The authors have no conflicts of interest to declare with regards to the contents of this study.

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