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Review article
Pregledni članak

LABORATORY DIAGNOSTICS AND QUALITY OF BLOOD COLLECTION

LABORATORIJSKA DIJAGNOSTIKA I KVALITET UZIMANJA UZORAKA KRVI

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Summary: Diagnostic blood samples collected by phlebotomy are the most common type of biological specimens drawn and sent to laboratory medicine facilities for being analyzed, thus supporting caring physicians in patient diagnosis, follow-up and/or therapeutic monitoring. Phlebotomy, a relatively invasive medical procedure, is indeed critical for the downstream procedures accomplished either in the analytical phase made in the laboratory or in the interpretive process done by the physicians. Diagnosis, management, treatment of patients and ultimately patient safety itself can be compromised by poor phlebotomy quality. We have read with interest a recent article where the authors addressed important aspects of venous blood collection for laboratory medicine analysis. The authors conducted a phlebotomy survey based on the Clinical and Laboratory Standard Institute (CLSI) H03-A6 document (presently replaced by the GP41-A6 document) in three government hospitals in Ethiopia to evaluate 120 professionals (101 non-laboratory professionals vs. 19 laboratory professionals) as regards the venous blood collection practice. The aim of this mini (non-systematic) review is to both take a cue from the above article and from current practices we had already observed in other laboratory settings, and discuss four questionable activities performed by health care professionals during venous blood collection.

Kratak sadržaj: Uzorci krvi za dijagnostiku uzeti pomoću flebotomije najčešći su od svih bioloških uzoraka koji se uzimaju i šalju u medicinske laboratorije na analizu, čime se pruža podrška nadležnim lekarima u postavljanju dijagnoze, praćenju i/ili terapijskom nadzoru bolesnika. Flebotomija, kao relativno invazivna medicinska procedura, zaista je presudna za postupke koji slede bilo u analitičkoj fazi u laboratoriji ili u procesu interpretacije koji obavljaju lekari. Loš kvalitet flebotomije može kompromitovati postavljanje dijagnoze, upravljanje pacijentom, njegovo lečenje i najzad bezbednost pacijenta. Sa zanimanjem smo nedavno pročitali članak u kom se autori bave važnim aspektima uzimanja uzoraka venske krvi za medicinske laboratorijske analize. Autori su sproveli anketu o flebotomiji zasnovanu na dokumentu H03-A6 (danas ga zamenjuje dokument GP41-A6) Instituta za kliničke i laboratorijske standarde (IKLS) u tri vladine bolnice u Etiopiji da bi ispitali 120 zaposlenih (101 nije bio laboratorijski radnik, dok 19 jesu bili laboratorijski radnici) o praksi uzimanja uzoraka venske krvi. Cilj ovog mini (nesistematičnog) pregleda je osvrt na sugestije iz pomenutog članka kao i na trenutne prakse koje smo već primetili u drugim laboratorijama, i uz to kratka diskusija o četiri problematične aktivnosti koje prilikom uzimanja uzoraka venske krvi obavljaju zdravstveni radnici. Ovo se odnosi na: i) procenu restrikcija u ishrani;

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We refer to: i) diet restriction assessment; ii) puncture site cleansing; iii) timing of tourniquet removal and; iv) mixing specimen with additives.

Keywords: blood specimen collection, patient safety, phlebotomy, medical errors, specimen handling, tourniquet

ii) čišćenje mesta punkcije; iii) vreme uklanjanja poveske i iv) mešanje uzoraka sa aditivima.

Ključne reči: uzimanje uzoraka krvi, bezbednost pacijenata, flebotomija, medicinske greške, rukovanje uzorcima, poveska

Introduction

The International Organization for Standardization (ISO 15189:2012 document) claims that necessary improvements and potential sources of non-conformities, either technical or concerning the quality management system, shall be systematically identified and corrected (1). The above standard deals with quality system requirements (i.e. quality indicators implementation) to be applied to the field of laboratory medicine, with a strong focus on patient safety (2). Quality indicators can be defined as objective measures developed and implemented to assess any critical health care segment such as patient safety (3, 4). Diagnostic blood samples collected by phlebotomy are the most common type of biological specimens drawn and sent to laboratory medicine facilities for being analyzed, thus supporting caring physicians in patient diagnosis, follow-up and/or therapeutic monitoring. Phlebotomy, a relatively invasive medical procedure, is indeed critical for the downstream procedures accomplished either in the analytical phase made in the laboratory or in the interpretive process done by the physicians. Diagnosis, management, treatment of patients and ultimately patient safety itself can be compromised by poor phlebotomy quality (5). We have read with interest a recent article where the authors addressed important aspects of venous blood collection for laboratory medicine analysis (6). The authors conducted a phlebotomy survey based on the Clinical and Laboratory Standard Institute (CLSI) H03-A6 document (presently replaced by the GP41-A6 document) (7). This survey evaluated 120 professionals (101 non-laboratory professionals vs. 19 laboratory professionals) as regards the venous blood collection practice in three government hospitals in Ethiopia (6). The aim of this mini (non-systematic) review is to both take a cue from the above article and from current practices we had already observed in other laboratory settings, and discuss four questionable activities performed by health care professionals during venous blood collection. We refer to: i) diet restriction assessment; ii) puncture site cleansing; iii) timing of tourniquet removal and; iv) mixing specimen with additives (*Table I*).

Table I Undesirable activities performed by professionals during venous blood collection.

Undesirable activities	Professional* (N, %)	p-value*
Diet restriction assessment	48, ~41%	0.057
Puncture site cleansing	37, ~31%	0.846
Timing of tourniquet removal	49, ~41%	0.057
Mixing specimen with additives	65, ~54%	<0.001

Legend: * N and (%) represent the total number of professionals that performed the undeliverable activities from the 120 professionals evaluated; p-values represent the difference from each undesirable activity between laboratory professionals and non-laboratory professionals reported. All dates presented in *Table I* were published by Melkie et al. (6).

Diet restriction assessment

The results published by Melkie et al. (6) showed that 41% of health care professionals do not assess properly diet restriction information from their patients. Kackov et al. demonstrated that a substantial proportion of patients do not come properly prepared to venipuncture, as specifically concerns fasting time (8). Fasting time assessment is really one the most important steps before performing the diagnostic blood specimen collection by venipuncture. In the hospital setting the most important question at patient admission should be »What time was your last food intake?« (9). With this information the laboratories could provide personalized blood collection during the hospitalization period, thus minimizing the variability due to the postprandial period, able to influence both diagnosis and follow-up (10, 11). Gathering this information would also allow physicians to promptly recognize the origin of abnormal laboratory data in non-fasting patients admitted with urgent conditions (e.g., most typically in the emergency department), in whom blood collection cannot be delayed for obvious reasons of providing timely care. Presently, an important framework for the harmonization of definitions for fasting requirements for laboratory tests was published by the Working Group on Preanalytical Phase (WG-PA) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) (12). Furthermore, analytical methods for laboratory diagnostic are strongly influenced by lipemia (13–15). Consequently, fasting time for all blood tests should be standardized at 12 hours, whenever compatible with the clinical setting (12).

Puncture site cleansing

The puncture site cleansing procedure is important because it prevents infection by skin microorganisms. To report the elevated frequency of undesirable cleansing procedures (31%), the authors considered

Table II The most important proposed changes to venipuncture procedure.

Step	CLSI H03-A6	Lima-Oliveira et al.
vi	Apply the tourniquet and select the venipuncture site and vein	Put on gloves
vii	Put on gloves	Cleanse the venipuncture site
viii	Cleanse the venipuncture site and allow to dry	Request the patient to just close his/her hand (never request the patient to »pump«)
ix	Perform venipuncture; once blood flow begins, request the patient to open his/her hand	Apply the tourniquet and select the venipuncture site and vein
x	Fill tubes using the correct order of draw	Perform venipuncture; once blood flow begins, request the patient to open his/her hand
		Also release and remove the tourniquet
xi	Release and remove the tourniquet	Fill tubes using the correct order of draw

Legend: The steps identification as regards the original CLSI H03-A6 standard (presently replaced by the GP41-A6 document). The comparison shown in this table was previously published (17).

»failure to wait until puncture site dry after application of an antiseptic«. This is rather obvious since they consider that when the antiseptic applied for cleansing the puncture site is not allowed to completely dry, it might then lead to spurious hemolysis (6). The outcome published by Salvagno et al. (16) showed that failure to wipe alcohol at the site of venipuncture should not be considered as a potential source of spurious hemolysis when drawing blood. As regards the CLSI H03-A6 document, the puncture site cleansing procedure should be done after tourniquet application (7). Presently, we proposed minor modifications in the blood collection procedure from the CLSI H03-A6 document, as pointed out in *Table II* (17). The new proposed procedure suggests cleansing the site before applying the tourniquet and locating a vein. From a practical phlebotomist's point of view (NKA, 34 years old), during the institutional training program some questions surfaced, such as: i) Can tourniquet application after cleansing the venipuncture site promote cross-contamination? ii) How can I decide the cleansing site before locating the most suitable vein by tourniquet application? As regards cross-contamination, the correct use of tourniquet does not allow bacteria or other pathogens that colonize the skin to contaminate the venipuncture site. Tourniquets should be applied between 7.5 and 10 cm above the venipuncture site. Moreover, single-use tourniquets are strongly recommended to avoid cross-contamination. Institutions that cannot use single-use tourniquets (e.g. because of cost savings) should clean the tourniquets with an antiseptic solution before use. In phlebotomy daily practices, more than 78% of diagnostic blood collection by venipuncture for outpatients is performed on the median cubital vein. Furthermore, based on the anatomical distribution of cutaneous veins and nerves, the median cubital vein in the upper arm near the radial cutaneous veins offers the site of minimal risk for venipuncture in the cubital region (18, 19). Therefore, we strongly suggest cleaning the entire cubital fossa before tourniquet application.

Timing of tourniquet removal

Several studies aimed to evaluate the influence of venous stasis by tourniquet application during the collection of diagnostic blood specimens by venipuncture (20–22). Briefly, the tourniquet-induced venous stasis promotes the outflow of water, diffusible ions and low molecular weight substances from the vessel, thus increasing the concentration of various blood analytes at the punctured site and potentially influencing interpretation of laboratory test results (*Figure 1*) (20). Moreover, when the vascular microenvironment is subjected to both hypoxia and concurrent stasis, endothelial cells are activated and may actively release a variety of compounds in the blood stream (e.g., tissue-type plasminogen activator). The accumulation of some bioproducts also ensues, such as protons that have the potential to promote changes in laboratory parameters (23). The most important analytes influenced by tourniquet application are shown in *Table III*. Our working group showed that the wide distribution and implementation of the CLSI H03-A6 document may be effective to improve the laboratory quality process as regards ISO 15189 standard, although the steps for collecting diagnostic blood specimens by venipuncture cannot be considered a gold standard so far, since inherent errors are still possible (i.e. variability as regards venous stasis) (24). Further, Bölenius et al. (25) observed only minor improvements in blood collection practices after one important educational intervention, especially regarding the hemolysis index (HI) as a quality indicator for hemolysis (26). This educational intervention was supported by laboratory instructors from the Country Council of northern Sweden focusing on rehearsal and implementation of the national and local venous blood specimen collection guidelines that are similar to international standards CLSI H03-A6 document (25). Obviously, educational programs and technological interventions for phlebotomists like those performed by Melkien et al. (6) and Bölenius et

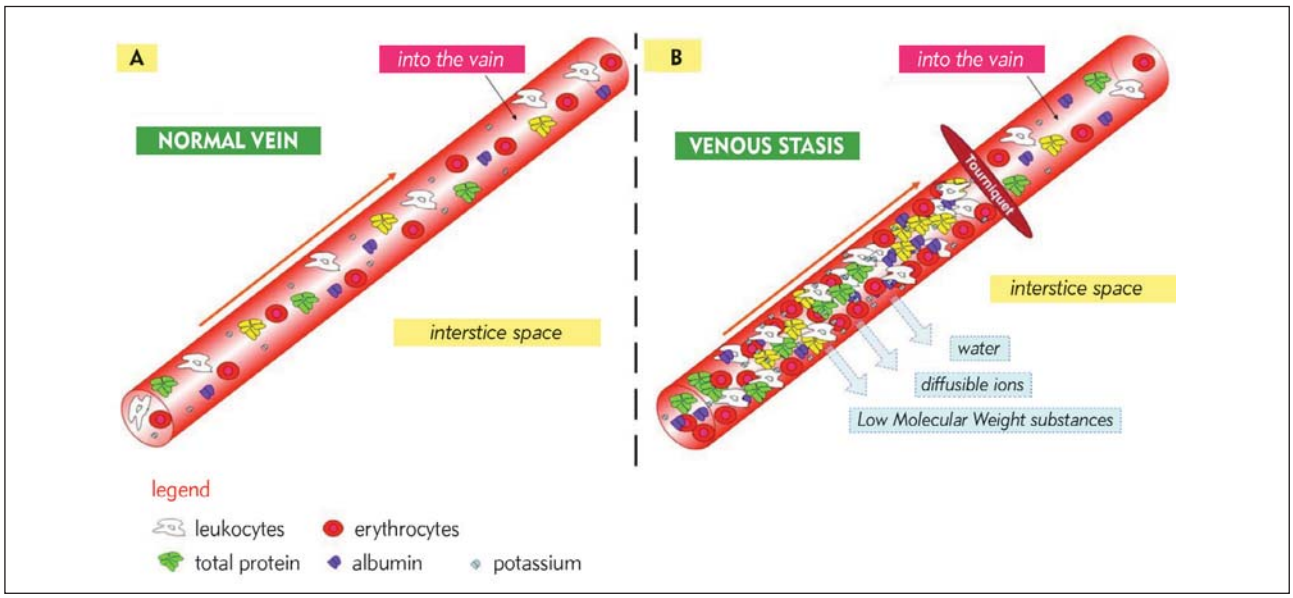

Figure 1 Schematic representation of the effects of stasis induced by tourniquet application on blood constituents.
Normal flow of blood through an unobstructed vein (*Figure 1-A*). The obstruction due to tourniquet reduces blood flow thus creating venous stasis (*Figure 1-B*) with net efflux of water from the vessel to the interstice. Elements of low molecular mass diffuse with water whereas high molecular weight compounds and cells concentrate in the vein.

Table III Impact of venous stasis by tourniquet application on routine laboratory tests (20–22).

	Tourniquet application time				
Tests	30 s	60 s	90 s	120 s	180 s
FIB	NS	NA	I	I	I
PT	NS	NA	NS	D	D
aPTT	NS	NA	NS	D	D
Glu	NS	I	I	I	D
TP	NS	I	I	I	I
ALB	NS	I	I	I	I
ALKP	NS	I	I	I	I
TG	NS	I	I	I	D
K	NS	I	I	I	I
Na	NS	NS	I	I	I
P	NS	NS	NS	NS	I
Ca	NS	I	I	I	I
Mg	NS	I	I	I	I
PLT	NS	I	I	I	I
RBC	NS	I	I	I	I
Hb	NS	I	I	I	I
Ht	NS	I	I	I	I
WBC	NS	I	I	I	I
NEU	NS	I	I	I	I
LYMP	NS	NS	I	I	I
MONO	NS	I	I	NS	NS
EOS	NS	I	I	NS	I
BASO	NS	NS	I	I	I

Legend: NS: not significant; I: increase; D: decrease; NA: not available; FIB: fibrinogen; PT: prothrombin time; aPTT: activated partial thromboplastin time; Glu: glucose; TP: total protein; ALB: albumin; ALKP: alkaline phosphatase; TG: triglyceride; K: potassium; Na: sodium; P: phosphate; Ca: calcium; Mg: magnesium; PLT: platelets; RBC: red blood cell; Hb: hemoglobin; Ht: hematocrit; WBC: white blood cells; NEU: neutrophils; LYMP: lymphocytes; MONO: monocytes; EOS: eosinophils; BASO: basophils.

al. (25) are relevant and could support quality improvement and guarantee patient safety (27–30). Maybe Melkien et al. (6) and Bölenius et al. (25) found a large number of non-conformities regarding tourniquet application time effects because strictly following the indications of the CLSI H03-A6 document would lead to an increase in tourniquet application time. Our working group showed that minor modifications in the procedure for diagnostic blood specimens collection by venipuncture of the CLSI H03-A6 document were however effective to reduce the tourniquet application time (17). The proposed new procedure for collection of diagnostic blood specimens by venipuncture should be strongly suggested for use by all quality laboratory managers and/or phlebotomy coordinators in their services, in order to avoid preanalytical errors regarding venous stasis and thus guarantee patient safety (17). Presently, the Croatian Society of Medical Biochemistry and Laboratory Medicine has published the national recommendations for venous blood sampling where appropriate tourniquet application is discussed and the recommendation for putting on gloves before tourniquet application is reported (5). A similar document was previously published by the Italian Society of Clinical Biochemistry and Laboratory Medicine, along with a phlebotomy checklist intended to minimize errors throughout the process of collecting blood (31–33).

Mixing specimens with additives

Suitable mixing of diagnostic blood specimens with additives immediately after blood collection is claimed to be effectively important, and is recommended by all vacuum tubes manufacturers' datasheets and CLSI documents (7, 34, 35). Parenmark and Landberg recently released a convincing paradigm about the mixing procedure of the diagnostic blood specimens. They showed that: i) mixing blood samples immediately after collection (on a horizontal mixing tray for 1 min, inverting 15 times) may not be mandatory for all types of tubes; and ii) instant mixing may produce spurious hemolysis and thereby introduce a bias for those parameters that are most susceptible to RBC injury (36). Based on Parenmark and Landberg outcomes, our working group evaluated the impact on quality of three different mixing procedures, in blood collected in K_2EDTA-, sodium citrate- and lithium heparin-containing vacuum tubes, by assessing 50 common laboratory tests. The evaluated procedures included: a) *Gold standard* – all diagnostic blood specimens were mixed gently and carefully, by five-time inversion as recommended by the manufacturer; b) *Rest time* – all diagnostic blood specimens remained 5 min at rest in an upright position, followed by gently and carefully mixing by five-time inversion; c) *No mix* – all diagnostic blood specimens were left in an upright position, without mixing afterwards. No fibrin filaments or micro clots were observed in any sample. Biases higher than the current desirable quality specifications derived from biological variations were only observed for sodium when procedure a) was compared with procedure b) and c). Thus, the mixing of blood specimens after collection with an evacuated tube system appears to be unnecessary under optimal conditions. The more reasonable explanation for these results would be that the blood turbulence generated by standard vacuum pressure inside the primary tubes is by itself sufficient to provide both solubilization, mixing and stabilization of additives and blood during venipuncture (37). Unfortunately, Melkie et al. (6) did not stratify the frequency of undesirable mixing of specimens from blood collection using a vacuum system or a syringe and needle. This kind of data analysis could support the quality managers and laboratory directors to organize training and continuous education plans worldwide. Furthermore, the apparently incorrect vigorous mixing of primary blood vacuum tubes does not appear to promote laboratory variability (38). As such, we can conclude that to avoid mixing primary blood tubes containing additives does not seem to introduce a bias in test results or to jeopardize patient safety.

All the aspects discussed in this mini and non-systematic review were previously considered by the CLSI, since the guidelines published by this non-governmental institute are definitely helpful for quality laboratory managers in their practices. The unique criticism about the CLSI H03-A6 document (presently replaced by GP41-A6) is that it was published in 2007, and in the following 6 years a considerable amount of data regarding the collection of diagnostic blood specimens by venipuncture has been published by independent researchers. Because of that, initiatives such as National Recommendations for Venous Blood Sampling (i.e. those prepared by the Croatian Society of Medical Biochemistry and Laboratory Medicine and the Italian Society of Clinical Biochemistry and Laboratory Medicine) are strongly encouraged. It is also noteworthy that the CLSI is reviewing the GP41-A6 document, and a novel version is expected soon, thus making everybody anxious in the wait of this new standard. The revision of the World Health Organization (WHO) guidelines on drawing blood is also ongoing (39). Expectedly, the WHO and CLSI documents should be updated according to the most recent information, and provide a set of indications that will be globally comparable to prevent further confusion around this essential health care practice.

Conflict of interest statement

The authors stated that have no conflicts of interest regarding the publication of this article.

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