NATIONAL HEMOPHILIA FOUNDATION

for all bleeding disorders

MASAC Document #262

MASAC RESOLUTION ON OFF-SITE HEMOSTASIS TESTING

The document was approved by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) on August 8, 2020, and adopted by the NHF Board of Directors on September 3, 2020.

In this present era of cost containment, more and more health insurance companies are contracting with large national laboratories to perform off-site hemostasis testing. Specifically, testing for relatively common conditions such as von Willlebrand disease (VWD) and hemophilia can be done in a laboratory cross-country, thousands of miles away from where the sample was drawn. While these laboratories are under strict College of American Pathology regulation for on-site analytic testing, pre-analytic variables at the stage of sample collection and processing can significantly affect the results often leading to artifactually low coagulation levels with a subsequent misdiagnosis of VWD or hemophilia.

This ongoing challenge of appropriate local blood sample collection and processing has been reported by several groups.[1-3] In particular, a delay in processing the sample in preparing platelet poor plasma within the hour of collection can lead to adsorption of von Willebrand factor (VWF) on the platelet surface in turn reducing the measurable VWF level.[3,4] Furthermore, crypoprecipitation of VWF and other proteins can occur if the blood sample is not transported to the laboratory at room temperature.[5] Also, refrigeration particularly of whole blood can lead to activation of Factor VIII and VWF: Ristocetin cofactor activity.[3,4]

In toto, these pre-analytic variables can lead to a misdiagnosis of a bleeding disorder. Recently Jaffray et al[2] enrolled females aged 12 to 50 years who had off-site specimen processing for VWF assays, and repeat testing performed at a consulting academic institution with onsite coagulation phlebotomy and processing. A total of 263 females from 17 institutions were included in the analysis. There were 251 subjects with both off-site and on-site VWF antigen (VWF:Ag) testing with 96 (38%) being low off-site and 60 (23%) low on-site; 223 subjects had VWF ristocetin co-factor (VWF:RCo) testing, 122 (55%) were low off-site and 77 (35%) were low on-site; similarly, 229 subjects had a Factor VIII (FVIII) assay at both sites and 72 (31%) were low off-site with less than half, 29 (13%) confirmed low by on-site testing. Higher proportions of patients had low VWF:Ag, VWF:RCo, and/or FVIII with off-site processing compared to onsite (McNemar's

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test P-value <.0005, for all assays). The implications of such a misdiagnosis of a bleeding disorder is considerable in terms of the added cost of additional testing, consultation to disprove the diagnosis, the psychosocial impact of first having an incorrect diagnosis often followed by screening of "affected" family members and the cost of inappropriate and potentially deleterious therapy. An over diagnosis may lead to overexposure to typical VWD therapies including high dose desmopressin and plasma derived VWF containing concentrates that may be given to a patient screened at an off-site laboratory collection site in preparation for a surgery or procedure prior to consultation with a hematologist.

At a time, of greater awareness of VWD based on upcoming VWD guidelines and prior MASAC advisories and from other organizations like the American College of Obstetrics and Gynecology[5] recommending testing for VWD in the setting of heavy menses, it is incumbent among caregivers of patients with potential bleeding disorders to be aware of potential artifacts inherent in send out hemostasis testing and that the misdiagnosis of a bleeding disorder can be reduced if a patient is referred for hemostasis testing where on site processing can be done in a timely fashion. MASAC advises that:

1. **If feasible, hemostatic evaluation should be performed at a hospital/Hemophilia Treatment Center/hemostasis laboratory capable of on-site processing in preparing the platelet poor plasma within one hour of collection and subsequent timely analysis or immediate freezing.**

2. **National laboratories that offer only off site hemostasis testing, should offer testing only at collection sites that have on-site processing capability in preparing the platelet poor plasma within one hour of collection.**

3. **In addition to documenting the time of collection of the sample, the time of processing the sample should be documented.**

4. **The language of the laboratory interpretation should include a caveat that artifactually low coagulation (VWF and FVIII) levels can be noted particularly in instances where there is a greater then one hour difference between the time of collection and the time of processing and that re-testing at on-site facility should be done.**

References:

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3. Favaloro EJ, Soltara S, McDonald J. Potential laboratory misdiagnosis of hemophilia and von Willebrand disease owing to cold activation of blood samples for testing. Am.J.Clin.Pathol 2004;122:668-692.
4. Bohm M, Taschner S, Kretzschmar E et al. Cold storage of citrated whole blood induces drastic time dependent losses in factor VIII and von Willebrand factor: potential for misdiagnosis of haemophilia and von Willebrand disease. Blood Coagul.Fibrinolysis 2006;17:39-46.
5. American College of Obstetricians and Gynecologists. ACOG committee opinion No. 451. Von Willebrand's disease. Obstet Gynecol 2009 Dec; 114(6);1439-43