Fall 2014

Hemophilia A: Pathophysiology and Treatment Strategies

Daniel Dinneen
Otterbein University, daniel.dinneen@otterbein.edu

Hemophilia A: Pathophysiology and Treatment Strategies

Dan Dinneen RN, BSN

Otterbein University, Westerville, Ohio

Introduction

Hemophilia is a sex-linked recessive coagulation disorder that varies in severity. The implications and complications of hemophilia can be life threatening; pathology is usually diagnosed during childhood and adequate management is essential in maintaining health. Advanced practice nurses treat a variety of hemophilia patients in varying roles throughout the lifespan as hemostasis is a constant physiologic process. Thorough knowledge of the pathophysiology, signs/symptoms, and treatment modalities related to hemophilia is necessary to provide the highest level of comprehensive medical care to such patients. Hemophilia care is continued throughout the lifespan, and newer research indicates that current treatment modalities can initiate further pathophysiologic processes that can require additional medical care and vigilance.

Pathophysiology

Hemophilia actually comprises several genetic abnormalities, resulting in altered production of either factors VIII (hemophilia A), IX (hemophilia B), or XI (hemophilia C) (Stoelting, 2012). Factors VIII, IX, and XI are proteins manufactured in the liver that are necessary in the clotting cascade and coagulation (Stoelting, 2012). Hemophilia A comprises the largest proportion of hemophilia cases, approximately 80-85% (Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., et. al., 2013).

Signs and Symptoms

- Common early manifestations are easy bruising in infancy with joint hematomas, upon development to the crawling/walking stages (Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., et. al., 2013). Bleeding can occur in multiple sites, and treatment is adjusted accordingly.
- See Tables 1 and 2 for breakdown of possible bleeding sites and their prevalence.

Table 1. Sites of Bleeding in Hemophilia, from: Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., et. al., 2013

Serious	Life-threatening
Joints (hemarthrosis)	Intracranial
Muscles, especially deep compartments (iliopsoas, calf, and forearm)	Neck/throat
Mucous membranes in the mouth, gums, nose, and genitourinary tract	Gastrointestinal

Table 2. Approximate Frequency of Bleeding at Different Sites, from: Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., et. al., 2013

Site of Bleeding	Approximate Frequency
Hemarthrosis: more common in hinged joints (ankles, knees, and elbows), less common in multi-axial joints (shoulders, wrists, and hips)	70-80%
Muscle	10-20%
Other major bleeds	5-10%
Central nervous system (CNS)	<5%

Underlying Pathophysiology

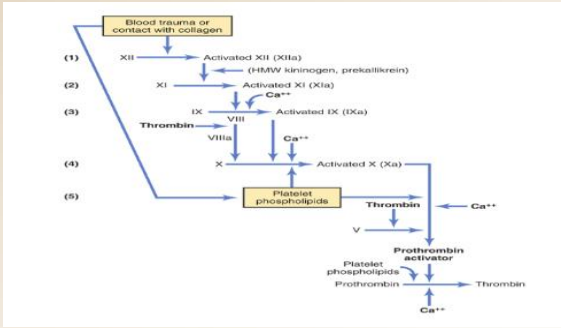
Hemophilia A is a sex linked recessive disorder that affects approximately 1 in 5,000 male births in Europe and North American (AnaesthesiaUK, 2009). The portion of the gene that correlates to factor VIII production is quite large, and severity of disease is linked to the portion of the gene affected; a functional factor VIII level 1% or less than normal results from drastic deletions of genetic material (Stoelting, 2012).

As previously mentioned, factor VIII is a protein produced in the liver that plays a major role in the intrinsic pathway of the clotting cascade, and is essential in activating factor X which causes the development of prothrombin and thrombin (Hall & Guyton, 2011). Without adequate coagulation and clot formation, hemostasis cannot be obtained and pathophysiologic bleeding ensues. Graphic representation of Factor VIII involvement in the clotting cascade is as follows in Figure 1.

Without development of thrombin and eventually fibrin, stable clot formation fails to occur as these proteins provide significant structural clot stability (Hall & Guyton, 2011).

Pathophysiology cont.

Figure 1. Intrinsic Pathway for Initiating Blood Clotting, from: Hall & Guyton, 2011.



Significance of Pathophysiology

As is the case with many disease processes, severity of Hemophilia A can be varied and directly correlational to the severity of factor VIII deficiency (Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., et. al., 2013). Table 3 illustrates the relationship of bleeding and factor level. As stated, factor VIII is critically important to the completion of the intrinsic coagulation pathway of hemostasis; without intrinsic activation, the sole means of adequate coagulation is dependent upon activation of the extrinsic pathway, namely factor VIIa (Hall & Guyton, 2011). Upon traditional laboratory evaluation, the activated prothrombin time is markedly increased as it clinically represents adequacy of intrinsic coagulation (Stoelting, 2012).

Unfortunately, additional pathology, development of factor VIII inhibitor, can develop in as many as 30-40% of patients with severe hemophilia A, less than 1% of functional factor VIII (Stoelting, 2012). Factor VIII inhibitors are IgG antibodies produced as an immune response to treatment with factor VIII replacement. Such inhibitors attach to factor VIII proteins resulting in its inactivation and hinder coagulation (Kasper, 2004). Source of factor VIII replacement; either plasma derived or recombinant generation, does not impact prevalence of inhibitor development (Kasper, 2004). Patients that develop factor VIII inhibitors are classified as either high or low responders, which directly correlates to level of inhibitor production (Kasper, 2004). Presence and extent of inhibitor development has significant impact upon clinical management of patients with hemophilia A (Kasper, 2004).

Table 3. Relationship of Bleeding Severity to Clotting Factor Level, from: Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., et. al., 2013

Severity	Clotting Factor Level	Bleeding Episodes
Severe	<1 IU/dL (<0.01 IU/mL) or <1% of normal	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge
Moderate	1-5 IU/dL (0.01-0.05 IU/mL) or 1-5% of normal	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Mild	5-40 IU/dL (0.05-0.40 IU/mL) or 5-<40% of normal	Severe bleeding with major trauma or surgery. Spontaneous bleeding is rare.

Implications for Nursing Care

At Risk Populations

Epidemiologic data suggest hemophilia A generally affects males, as it is a sex linked recessive disorder. Signs and symptoms usually are related to ease of bruising/hematoma formation early in the lifespan especially during the crawling/walking phase of development (Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., et. al., 2013). The majority of cases are hereditarily linked, but 1/3 of new cases are the result of spontaneous genetic mutation without prior family history (Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., et. al., 2013).

Prophylactic Treatment

Patients with hemophilia A are generally prophylactically treated with intravenous factor VIII with a goal of maintaining factor VIII levels at approximately 1 IU/dL as this level is associated with significantly decreased risk of spontaneous bleeding (Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., et. al., 2013). The primary goal of hemophilia A treatment through early adulthood is to maintain/preserve musculoskeletal function and prevent any other source of major bleeding (Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., et. al., 2013).

Acute Management of Bleeding

First line treatment of patients with hemophilia A is intravenous factor VIII replacement, and Table 4 represents The World Federation of Hemophilia's recommended initial target factor VIII levels for specific bleeding processes.

Table 4. Suggested Plasma Factor Peak Level and Duration of Administration, from: Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., et. al., 2013

Type of Hemorrhage	Desired Level (IU/dL)	Duration Days
Joint	10-20	1-2
Superficial muscle	10-20	2-3
Deep muscle	20-40	3-5
CNS/head	50-80	1-3
Throat/neck	30-50	1-3
Gastrointestinal	30-50	1-3
Renal	20-40	3-5
Surgery (major)	60-80 (pre-op)/30-40 (post-op)	1-3
Surgery (minor)	40-80 (pre-op)/20-50 (post-op)	1-5

Additional Considerations/Modalities for Managing

- If administered factor VIII via plasma or recombinant source fails to increase serum factor VIII levels; the patient must be assessed for the presence of inhibitors/antibodies (Kasper, 2004).
- If acute bleeding cannot be controlled by the administration of factor VIII, administration of FFP, activated factor VII, and activated prothrombin complex is indicated to achieve hemostasis (Kasper, 2004).
- Tranexamic acid is an adjunct that can be administered, orally or intravenous, in addition to factor VIII to promote adequate hemostasis by preventing fibrin degradation ((Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., et. al., 2013).

Conclusion

Hemophilia A is a disease requiring medical care throughout the lifespan with the possibility of acute exacerbations and accompanying serious illness and disability. As advancements in medical treatment occur, vigilance is needed to adequately manage such patients and ensure their health and wellness. Primary treatment is focused on replacing Factor VIII levels and constant collaboration amongst the entire healthcare team and patient.

References

AnaesthesiaUK. (2009). Haemophilia. Retrieved from http://www.frca.co.uk/article.aspx?articleid=100098

Batorova, A., Morongova, A., Tagariello, G., Jankovicova, D., Prigancova, T., & Horakova, J. (2013, October). Challenges in the Management of Hemophilia B with Inhibitor. *Seminars in thrombosis and hemostasis* (Vol. 39, No. 07, pp. 767-771). Thieme Medical Publishers.

Collins, P. W., Fischer, K., Morfini, M., Blanchette, V. S., & Björkman, S. (2011). Implications of coagulation factor VIII and IX pharmacokinetics in the prophylactic treatment of haemophilia. *Haemophilia*, *17*(1), 2-10.

Gouw, S. C., van den Berg, H. M., Fischer, K., et. al. (2013). Intensity of factor VIII treatment and inhibitor development in children with severe hemophilia A: the RODIN study. *Blood*, *121*(20), 4046-4055.

Hall, J. E., & Guyton, A. C. (2011). *Guyton and Hall textbook of medical physiology* (12th ed.). Philadelphia, Pa: Saunders/Elsevier.

Kasper, C. K. (2004). Diagnosis and management of inhibitors to factors VIII and IX. *Treatment of Hemophilia Monograph. World Federation of Hemophilia*.

Mathews, V. (2012). Management of Hemophilia. *Practical Pediatric Hematology*, *1551*, 6-30.

Srivastava, A., Brewer, A. K., Mauser-Bunschoten, E. P., et. al. (2013), Guidelines for the management of hemophilia. *Haemophilia, 19*(1)e1–e47. doi: 10.1111/j.1365-2516.2012.02909.x

Stoelting, R. K. (2012). *Stoelting's anesthesia and co-existing disease* (6th ed.). Philadelphia: Churchill Livingstone/Elsevier.

Tran, H. T. T., Sørensen, B., Rea, C. J., Bjørnsen, S., Ueland, T., Pripp, A. H., & Holme, P. A. (2014). Tranexamic acid as adjunct therapy to bypassing agents in haemophilia A patients with inhibitors. *Haemophilia*, *20*(3), 369-375.

OTTERBEIN UNIVERSITY