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Review Article

Evaluating the Predictive Value of Activated Partial Thromboplastin Time Test in Monitoring Factor VIII Therapy in Hemophilia A Patients

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Abstract

Hemophilia A is the most common hereditary coagulation disorder, resulting from a deficiency of clotting Factor VIII, which increases the risk of excessive bleeding and bruising. As an inclusive treatment, Factor VIII replacement therapy is given in the management of Hemophilia A. Prophylaxis has become the primary treatment, focusing on maintaining a baseline Factor VIII level to proactively prevent bleeding episodes. While this therapy has significantly improved patient outcomes, a major challenge remains in determining its efficiency over time. Factor VIII levels tend to decline unpredictably. The standard method for monitoring Factor VIII levels involves Factor assay, but the high cost and limited availability make routine use impractical, especially in resource-limited settings. This uncertainty in monitoring therapy effectiveness leaves patients vulnerable to spontaneous bleeding episodes and complicates clinical decision-making regarding optimal dosing intervals. Given this challenge, an alternative, cost-effective method is necessary to predict the efficiency of Factor VIII replacement therapy. This review aimed to explore the potential use of the activated partial thromboplastin time test (aPTT) as a predictive marker for Factor VIII decay. By establishing a correlation between aPTT and Factor VIII levels, a practical and accessible diagnostic approach can be developed to optimize treatment regimens. Additionally, this review aimed to assess the ability of aPTT to predict Factor VIII levels in Hemophilia A patients, emphasizing the significance of diagnostic strategies in enhancing patient outcomes and ensuring more efficient use of therapeutic resources.

List of abbreviations

aPTT – Activated Partial Thromboplastin Time
FVIII – Factor VIII
NHSL – National Hospital of Sri Lanka
SPSS – Statistical Package for the Social Sciences

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1. Introduction

1.1. Hemophilia A

Hemophilia A is the most common hereditary coagulation disorder caused by a deficiency of clotting Factor VIII [1, 2]. This condition predominantly affects males, with an estimated global incidence of 1 in 5000 live male births [3], while in Sri Lanka, the occurrence rate is approximately 1 in 20,000 cases [4]. Based on the amount of Factor VIII activity in the blood, Hemophilia A is classified into three categories. Severe Hemophilia A, which has less than 1% Factor VIII activity. Moderate Hemophilia A with Factor VIII activity ranging from 1% to 5%, Mild Hemophilia A with 5–40% activity [5]. The disorder arises from genetic mutations affecting the production of clotting factors, leading to impaired blood clotting and an increased risk of excessive bleeding and bruising [6, 7].

Given the significant clinical burden of Hemophilia A, accurate diagnosis and effective management strategies are crucial. Diagnosis involves a thorough physical examination, including an assessment of medical and family history, along with laboratory tests to evaluate coagulation function [8]. Routine coagulation tests such as Bleeding Time (BT), Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), and Thrombin Time (TT) help assess the efficiency of clotting pathways [9, 10]. Among these, aPTT is particularly important in screening Hemophilia A patients, as it measures the intrinsic pathway and is typically prolonged due to Factor VIII deficiency [11]. Confirmatory tests, including Factor assays, mixing studies, and genetic testing, provide definitive diagnosis.

The primary approach to managing Hemophilia A is through Factor VIII replacement therapy, which involves administering clotting Factor concentrates to prevent or control bleeding episodes [12]. Additionally, emerging treatments such as gene therapy [13] and non-replacement therapies, including Hemlibra, are being explored. Antifibrinolytics, such as tranexamic acid, and hormonal therapies also contribute to bleeding management in specific patient populations [14]. Prophylaxis, which aims to maintain baseline Factor VIII level, has become the standard treatment to prevent spontaneous bleeds and long-term joint damage [15].

Despite the effectiveness of Factor VIII replacement therapy, a major challenge remains in determining the duration of its efficacy, as Factor VIII levels decline over time. Currently, Factor VIII assay are the gold standard for monitoring Factor VIII levels, but the high cost and the irregular attendance of patients at clinics limit their routine use. Consequently, patients often face uncertainty regarding the optimal timing for their next dose, increasing the risk of uncontrolled bleeding and treatment adherence issues.

Addressing this challenge requires an alternative, cost-effective approach to predict the efficiency of Factor VIII replacement therapy. Establishing a correlation between aPTT and Factor VIII levels could serve as a promising diagnostic tool. This approach would enhance patient management, reduce the risk of bleeding episodes, and improve overall quality of life for individuals with Hemophilia A. Therefore, our review aims to explore the efficiency of Factor VIII replacement therapy for Hemophilia A patients and investigate the potential use of aPTT as a predictive marker for assessing the effectiveness of Factor VIII replacement therapy. By examining current treatment strategies and evaluating the feasibility of using aPTT in routine clinical practice, this review seeks to provide valuable insights for optimizing Hemophilia A management and improving patient outcomes.

1.2. Hemophilia A and Epidemiology

Hemophilia is a genomic disorder that affects blood clotting, which is necessary to stop bleeding after an injury. It is the most common hereditary coagulation factor deficiency [16, 17]. Hemophiliacs are susceptible to bleeding episodes, such as spontaneous bleeding into joints, muscles, and organs, as well as protracted bleeding following wounds or operations [18]. The severity of hemophilia varies, depending on the level of clotting factor deficiency, with severe hemophilia resulting in more frequent and severe bleeding episodes [5]. Females are the carriers of this inherited condition, but it most often affects males. According to the data of the World Federation of Hemophilia, in 2003, it was estimated that 400,000 patients with hemophilia were expected globally [19]. Hemophilia A affects approximately 1 in 5,000-10,000 males worldwide. Hemophilia B affects approximately 1 in 20,000-34,000 males worldwide [20]. Sri Lanka has an incidence rate of 1 in 20,000 for hemophilia, which would mean approximately 2,100 patients [21, 22]. However, most mild and moderate cases may go undiagnosed. There are currently 1,300 registered cases, with clinics at the National Hospital and Lady Ridgeway Hospital providing support [4, 23].

1.3. Molecular pathology and pathophysiology of Hemophilia A

Hemophilia A is caused by mutations in the genes that encode Factor VIII, resulting in reduced or absent production of these clotting Factors [2, 24]. Liver cells produce and secrete Factor VIII, they are inactively circulating in the blood prior to being activated by cleavage with certain enzymes [25, 26]. In Hemophilia A, mutations in the Factor VIII gene impair the synthesis or stability of Factor VIII, resulting in decreased activity of this clotting Factor. These deficiencies in clotting Factor activity led to impaired coagulation and increased bleeding [5]. The disease is inherited through the X chromosome, so men with a defective FVIII gene will pass the abnormal X chromosome to their daughters and a normal Y chromosome to their sons. Female carriers have a 50% risk of passing on the carrier condition to their daughters and a 50% chance of passing the disease on to their sons [6, 7, 27].

Men are more likely than women to be affected by Hemophilia A due to the fact that they only have one X chromosome. Females can be carriers of Hemophilia A, meaning they have one mutated X chromosome and one normal X chromosome, but usually do not experience significant bleeding symptoms [7, 28]. Spontaneous bleeding into joints, muscles, and soft tissues, as well as prolonged bleeding after injuries or surgeries, are the characteristics of Hemophilia A. This leads to articulations and recurrent joint hemorrhages because of a disabling disorder called hemophilic arthroplasty [29].

1.4. Diagnosis of Hemophilia A

Clinical examination

A thorough physical examination is essential for the diagnosis of Hemophilia A. The examination should include an assessment of the patient's medical and family history and a physical examination to identify any signs of bleeding or bruising [8]. The clinical examination of Hemophilia A involves assessing bleeding symptoms and using imaging tests to evaluate joint damage and disease progression [30, 31]. Susceptibility to bleeding episodes, such as spontaneous bleeding into joints, muscles, and organs, as well as protracted bleeding following wounds or operations, are also done to examine Hemophilia A [31, 32].

Laboratory investigations

Laboratory diagnosis of Hemophilia A involves testing for abnormalities in clotting Factor levels and coagulation pathways [9]. Laboratory testing for coagulation measures the speed at which blood clots form after the coagulation cascade starts. Common tests include Bleeding time (BT), Prothrombin time (PT), Activated partial thromboplastin time (aPTT), and Thrombin time (TT) to evaluate the extrinsic and intrinsic pathways of coagulation [29, 33]. PT test calculates the time it takes for the blood to clot. This test detects the activity of the tissue Factor pathway-initiated extrinsic pathway of the coagulation cascade. In Hemophilia A patients, PT is typically normal since Factors involved in the extrinsic pathway (Factors VII, X, and V) are not affected in Hemophilia A [10, 30]. aPTT test is a commonly used diagnostic test for Hemophilia A [8]. It measures the time it takes for blood to clot after a series of substances (activators) are added to the blood sample [11]. The purpose of this test is to measure the activity of the intrinsic pathway in the coagulation cascade, which involves Factors VIII, IX, XI, and XII. aPTT is typically prolonged in Hemophilia A patients.

The confirmatory tests for Hemophilia A include Factor assays, Mixing studies, and Genetic testing [34, 35]. Factor assays; Measure the levels of specific coagulation Factors in the blood. Low levels of Factor VIII confirm Hemophilia A. In a mixing study, the patient's plasma is combined with normal plasma to check for the presence of a coagulation factor deficiency. If the clotting time improves after mixing, it suggests a coagulation Factor deficiency is present [1, 30]. Genetic testing is another method used to confirm a diagnosis of Hemophilia A by identifying mutations in the genes responsible for producing coagulation Factors [36].

The study conducted by [37] has demonstrated that various laboratory assays used for diagnosing and monitoring Haemophilia A are significantly affected by different therapies. They discovered that the one-stage clotting assay, which is commonly used for measuring Factor activity, shows discrepancies when applied to patients receiving extended half-life Factor concentrates and gene therapy. Similarly, the chromogenic substrate assay, though more specific in some cases, also exhibits variations depending on the Factor replacement product used.

1.5. The role of aPTT in Hemophilia A patients

aPTT is a commonly used screening test for Hemophilia A, and it measures the intrinsic pathway of the coagulation cascade [38]. In Hemophilia A patients, aPTT is typically prolonged due to the deficiency of factor VIII. A Study conducted by [11], aPTT is a common laboratory test to evaluate the intrinsic pathway of the coagulation cascade, which is the pathway typically affected in Hemophilia A. It further explains that aPTT can be used as a tool for monitoring the response to factor VIII replacement therapy in Hemophilia A patients and it can help to determine the appropriate dosage of factor VIII to be administered, as well as the frequency of infusions [39]. In addition, aPTT can be used to monitor the effectiveness of factor VIII replacement therapy and identify patients who may require additional treatment [11].

1.6. Treatments for Hemophilia A

In the management of Hemophilia A, several critical facts are considered to determine the most appropriate method of treatment. These facts include the severity of the disease, baseline residual Factor activity, personal or family history, and previous hemostatic challenges [40]. By carefully evaluating and integrating these facts, healthcare professionals can develop a comprehensive management plan that addresses the unique needs and circumstances of each individual with Hemophilia A [33].

Factor Concentrates

Hemophilia A is mostly treated by clotting Factor concentrates infused into the patients [12]. When specific single-factor concentrates are available, they are the preferred treatment for Hemophilia A [15]. Plasma-derived products are commonly used. In the absence of specific Factor concentrates, Fresh Frozen Plasma (FFP), Cryoprecipitate, and Prothrombin Complex Concentrates (PCCs) are used as alternate sources for Factor replacement. Some newer clotting Factor concentrates have been developed with extended half-life properties. These products can last longer in the bloodstream, allowing for less frequent infusions while maintaining effective Factor levels [40].

Gene therapy

Gene therapy is a developing treatment option for Hemophilia A [41]. In gene therapy, the patient's cells are given a functional copy of the defective gene that produces Factor VIII. This method aims to enable the body to produce its clotting Factor continuously, potentially providing a long-term cure for the disorder. This study [42] explores the potential of gene therapy for Hemophilia A using adeno-associated viral (AAV) vectors to enable endogenous Factor VIII production. Clinical trials demonstrated that a single intravenous administration of AAV vectors led to sustained Factor VIII expression, reducing bleeding episodes and minimizing the need for frequent Factor replacement. While some patients achieved near-normal Factor VIII levels, challenges such as immune responses causing transient liver inflammation and a gradual decline in expression remain. Despite these limitations, gene therapy represents a major advancement in Hemophilia A treatment, with the potential to provide long-term benefits and reduce dependence on traditional therapies. Further research done by [43] has confirmed that gene transfer to the liver via AAV vectors can achieve therapeutic or even curative outcomes. While immune responses to the viral capsid pose a challenge, transient immunosuppression strategies have been developed to mitigate this.

Other treatments

In addition to Factor concentrates and Gene therapy, there are other treatments used in managing Hemophilia A. One type is antifibrinolytics like tranexamic acid, which help stop bleeding [40] are used for less severe bleeding in areas like the mouth, minor procedures, and heavy menstrual bleeding. This systematic review and meta-analysis by [44] evaluated the effectiveness of antifibrinolytic therapy in preventing postoperative bleeding in hemophilia patients undergoing dental extractions. Using PRISMA guidelines, the study analyzed randomized controlled trials comparing the systemic administration of tranexamic acid and aminocaproic acid to placebo. The findings demonstrated an 84% reduction in the risk of postoperative bleeding among patients receiving antifibrinolytics. [45] evaluated the effectiveness of antifibrinolytic therapy in preventing oral bleeding in patients with hemophilia or Von Willebrand disease undergoing minor oral surgery or dental extractions. The study analyzed randomized controlled trials comparing tranexamic acid (TXA) and epsilon aminocaproic acid (EACA) with placebo. Hormonal therapies, either taken by mouth or applied locally, can be effective in managing heavy menstrual bleeding in hemophilia patients [40]. These therapies are used to reduce bleeding and enhance the quality of life for Hemophilia A patients. Hormonal therapy has been explored as a potential approach to managing bleeding in Hemophilia A, particularly in female carriers who experience heavy menstrual bleeding. Estrogen-based treatments, including oral contraceptives, have been shown to increase Factor VIII and von Willebrand Factor levels, thereby reducing bleeding tendencies [46]. Studies suggest that hormonal therapy can help stabilize clotting mechanisms in symptomatic carriers and patients with mild Hemophilia A. However, its effectiveness is limited to specific cases, and it does not replace conventional factor replacement or gene therapy approaches [46, 47]. New non-replacement therapies, such as Hemlibra, show promise for treating Hemophilia A [40]. They promote thrombin generation by mimicking the activity of certain clotting Factors [48]. Other approaches, like inhibiting natural anticoagulants or using engineered molecules, are being explored. These therapies have shown favorable safety profiles and effectiveness in patients with coagulation disorders. However, their role in other rare bleeding disorders requires further investigation. The study [48] assessed the availability, acceptance, and clinical outcomes of Hemlibra, a bispecific monoclonal antibody that mimics Factor VIII function. Based on a 2020 European survey of hemophilia treatment centers, Hemlibra was widely used, with 100% of inhibitor patients and 88% of non-inhibitor patients having access. The drug desmopressin has the ability to encourage the patient's body to release stored Factor VIII. It is most effective in patients with mild Hemophilia A or some cases of moderate Hemophilia A. It is often used for minor bleeding episodes or before dental or minor surgical procedures. The study [49] explores the role of desmopressin (DDAVP) in managing Hemophilia A, particularly in patients with mild to moderate disease. Desmopressin, a synthetic analogue of vasopressin, stimulates the release of stored Factor VIII, increasing plasma Factor VIII levels 2-3 times above baseline. Initially used for minor surgeries like dental extractions, its effectiveness has been confirmed in major procedures as well.

Factor VIII replacement therapy

In Factor VIII replacement therapy, the absence or deficient clotting Factor is replaced with synthetic or recombinant Factor VIII concentrates that are given intravenously [43]. This helps to restore the clotting cascade and avoid or control bleeding episodes. With less danger of bleeding [15], Hemophilia A patients now have a far better prognosis and can lead healthier lives because of this treatment. Recombinant technology is used to make Factor concentrates, or they can be made from human plasma [50]. In order to manage bleeding episodes and lower the risk of bleeding again, Factor VIII replacement therapy assists in restoring the patient's blood with the deficient clotting Factor [51]. On-demand treatment involves administering clotting Factor concentrates as needed when bleeding occurs [52]. This approach is commonly used for milder cases of Hemophilia A or for patients who prefer a more flexible treatment schedule. However, it may not be as effective in preventing long-term joint damage compared to prophylactic treatment [53].

1.7. Prophylaxis as the Standard Treatment for Hemophilia A

Primary prophylaxis is recognized as the first-line treatment for Hemophilia A. Starting prophylaxis can help avoid joint deterioration and improve the patient's quality of life [54]. It's routinely recommended for severe Factor VIII deficiency due to the risk of serious bleeding events, even in adulthood [55]. Prophylaxis involves systematic administration of clotting Factor concentrates to proactively prevent the occurrence of bleeding episodes [56]. This approach is especially recommended for severe hemophilia A patients to maintain a higher level of Factor VIII in their blood and prevent joint damage and other complications associated with frequent bleeding [54–56].

1.8. Correlation between Factor VIII Replacement Therapy and aPTT values

Factor VIII replacement therapy involves administering clotting Factor concentrates on patients with hemophilia A to correct the deficiency. Before factor VIII replacement therapy, the aPTT is usually prolonged due to the deficiency of factor VIII [52]. As factor VIII activity increases following treatment, the aPTT values will begin to normalize. With successful replacement therapy, the aPTT will be within normal range, indicating improved coagulation function. The degree of aPTT correction will depend on the amount and efficacy of the administered factor VIII concentrate [57]. The study conducted by Zoysa [58] has performed correlation bivariate analysis to identify a relationship between aPTT and the time from the latest Factor treatment to the collection of blood (T). It has been observed that there is a strong, significant positive correlation between aPTT and T ($r=0.820$; $p=0.000$). Most of the studies done on the measurement of Factor VIII activity used aPTT for diagnosis and related treatments in Hemophilia A patients [59, 60] revealed that aPTT acts as a predictor of Factor VIII levels in Hemophilia A patients, and elevated aPTT has a strong correlation to Factor VIII deficiency in Hemophilia A patients. In the study, Zoysa [58] established a cutoff value for aPTT as an indicator of Elevated Factor VIII levels due to the Factor VIII replacement therapy dose in the body; ROC curves were employed by utilizing information on elevated Factor VIII levels resulting from administered doses and their corresponding aPTT values. According to the ROC analysis, the cut-off value of aPTT is estimated to be 38.8 s with a sensitivity of 95.2% and specificity of 37.2%. Given the estimated cutoff value for aPTT at 38.8 (approximately 39) seconds, results show with a considerable AUC (0.603) that an aPTT exceeding 39 seconds indicates a Factor VIII level in the body below 25%. Conversely, an aPTT below 39 seconds indicates a Factor level higher than 25%. Similar studies were carried out using ROC curve analysis to establish a predictive relationship between Factor XII levels and aPTT [61] and to determine the cutoff value of aPTT for Factor VIII inhibitor [62, 63].

1.9. aPTT as a predictive marker for the efficiency of Factor VIII replacement therapy

The study conducted by Zoysa [58] performed a Kaplan–Meier survival analysis to predict the efficacy of Factor VIII replacement therapy in individuals with Hemophilia in order to find out the maximum number of days of recurrences after the latest Factor VIII administration. For that, aPTT values and the time from the latest Factor treatment to the collection of blood were used. The recurrence: i.e. timeframe during Factor VIII levels boosted by the therapy, return to a state of deficiency (prolonging aPTT or recurrence) is around 08 days and initially starts within 5 days & complete recurrence in 11 days according to the mean. As the data reveals diverse variations in the time from the latest factor treatment to the collection of blood, ranging from days to hours, they suggest the median value over the mean value that gives the recurrence is around 05 days and initially starts within 02 days & complete recurrence in 08 days. Similarly, the Kaplan–Meier survival analysis was used to evaluate the Complete Remission (CR) of therapeutic options such as immune suppressive therapy and targeted therapy in patients with AHA [64, 65]. Using the Kaplan–Meier curves, [64] have found that it took 40 to 60 days to complete remission occur, depending on the type of immuno-suppressive therapy used. Another similar study done by [65] to find the use of bevacizumab as a therapeutic option for Acquired Hemophilia A, have used Kaplan–Meier survival analysis, and they observed the CR within a median duration of 115 days for various Factor levels. Another instance where Kaplan– Meier survival analysis was used was to investigate the relationship between Factor VIII activity and bleeding risk during prophylaxis for severe Hemophilia A patients [36]. Kaplan-Meier plots were employed to analyze the time to the first spontaneous bleeding event over a fixed period of 60 days. The analysis revealed that the duration until the occurrence of the initial spontaneous bleeding event was extended during periods characterized by higher levels of Factor VIII.

2. Conclusion

The study explored the potential of aPTT as a marker for predicting the efficiency of Factor VIII replacement therapy. Previous attempts to establish a correlation between aPTT and Factor VIII levels were reviewed, highlighting the significance of such an association. Utilizing aPTT, a widely available and cost-effective laboratory test, could provide an alternative method for estimating Factor VIII levels without the need for specialized Factor assays. Furthermore, the study examined approaches that assessed the effectiveness of Factor VIII replacement therapy using aPTT, particularly through Kaplan-Meier survival analysis. This approach offers valuable insights into the recurrence of Factor VIII deficiency, aiding in clinical decision-making for Hemophilia A patients. By improving the prediction of treatment efficacy, this method addresses critical challenges such as spontaneous bleeding, the risk of bleeding, and uncertainty regarding the timing of subsequent doses, ultimately enhancing patient management and care.

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Article Information

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