Hemophilia Care in India: A Review and Experience from a Tertiary Care Centre in Uttar Pradesh

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Abstract Approximately 14,000 people with hemophilia are registered at the Hemophilia Federation of India; however, hemophilia remains under-diagnosed and many cases are not registered. In June 2009, the Government of Uttar Pradesh made anti-hemophilic factors available at a few centers, including the Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow. Consequently, the level of hemophilia care has improved considerably in recent times. Amongst the many challenges facing people with hemophilia, the development of inhibitors, which neutralize clotting factors provided by replacement therapy, is the most feared one. Healthcare professionals who treat people with hemophilia should not only be knowledgeable about the condition and committed to bettering the management of hemophilia, but also take responsibility for the judicious allocation of resources for various aspects of managing hemophilia. This manuscript aims to raise awareness regarding the detection and management of inhibitors in hemophilia based on the experience of a tertiary care hemophilia treatment centre in Uttar Pradesh, India.

Keywords Hemophilia · Diagnosis · Inhibitors management · Bypassing agents · India

Introduction

Hemophilia treatment in India is currently coming of age and poised to enter the mainstream healthcare agenda.

Although there are some active centers providing treatment to people with hemophilia (PWH), including surgical treatments, they remain too few, and their functioning is constrained by the cost of anti-hemophilic factors. Support groups for hemophilia patients have also contributed greatly to creating awareness amongst patients and organizing treatment facilities. In the last few years, some state governments have started financing anti-hemophilic factors, making them freely available at some centers. This has opened a new chapter for the management of hemophilia in India. As diagnosis and treatment improve, treating clinicians are facing new challenges such as the management of PWH who develop inhibitors and the judicious allocation of resources for managing the various aspects of hemophilia. It is mandatory to collect data about patients: their geographical location, confirmation of diagnosis, and assessment of inhibitors. These data are required for better planning and structuring of hemophilia care services by enabling more efficient use of government funds for distribution of not only anti-hemophilic factors but also safe bypassing agents, which are used to manage hemophilia with inhibitors.

This manuscript aims to contextualize the burden of inhibitors in hemophilia and to raise awareness about the diagnosis and management of this condition through the experience of a tertiary care hemophilia treatment centre in Uttar Pradesh, India.

Hemophilia in India: Overview

Hemophilia is an X-linked hereditary bleeding disorder, leading to deficiency of factor VIII (FVIII) or factor IX (FIX). This deficiency results in recurrent bleeds into joints

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and muscles, leading to hemophilic arthropathy and contractures [1].

It is estimated that 10–80% of PWH are present in developing countries such as India [2]. However, hemophilia cases remain under-diagnosed, and many cases are not registered. Given that the incidence of hemophilia A is one in 5,000 and hemophilia B is one in 30,000, as in the US [3], one expects India to have close to 100,000 PWH. However, according to the most recent survey published by the World Federation of Hemophilia [3], with data provided by the Hemophilia Federation of India (HFI), only 13,448 patients are registered [3].

In developed countries, the concept of comprehensive care for PWH is defined as an ongoing process involving all medical and psychosocial aspects affecting PWH and their families. It also carries a strong element of defining better treatment or the preventive approach. With this model, hemophilia has shifted from a life-shortening disease to a lifelong disease [4]. Nevertheless, the cost of managing hemophilia remains a concern, particularly in developing countries.

Despite India's rapid economic growth and technological advancements, primary healthcare remains lacking. PWH lack health insurance because they cannot afford private health insurance and because hemophilia remains classified as a low-volume, high-cost disease [5]. In India, the economic conditions of PWH drive treatment decisions, and only a few patients have access to factor replacement therapy. Most PWH rely only on RICE (Rest, Ice, Compression, and Elevation), adjunct therapies such as epsilon-aminocaproic acid (EACA), tranexamic acid, and wet products such as fresh frozen plasma (FFP) and cryoprecipitate whenever available [6].

When it comes to diagnosis and treatment, PWH still do not have adequate options or opportunities within India. For example, coagulation laboratories are not available in a standardized fashion. According to Ghosh et al. (2010) [5], the majority of district hospitals and even medical colleges do not have coagulation screening facilities, which impacts diagnosis of new cases. Facilities for screening for and confirming the presence of inhibitors are extremely scarce. Further, the few available laboratory facilities need regular external quality assessment to improve their performance [2]. The poor availability of diagnostic and treatment facilities along with the lack of awareness about hemophilia amongst primary care physicians and specialists is a major impediment for the management of hemophilia. Consequently, a diagnosis of hemophilia is not suspected in certain situations. Many hemophilia cases with complications are treated as cases of arthritis, and many are treated surgically because they have been misdiagnosed as cases of appendicitis or acute abdomen if there is an iliopsoas bleed or intra-abdominal bleed. Young children with intracranial

bleeds are operated upon without testing their coagulation ability, and hemophilia is only suspected 2–3 days after surgery when bleeding continues despite the surgeon's desperate attempts to stop the bleeding.

In a convenience sample of 148 patients with severe hemophilia, physical disability was present in 79 and 68% patients who were >25 years old and between 13–24 years, respectively [7]. These high disability rates have a severe negative impact on productivity and the patient's ability to have a successful job or career. Disease unawareness and lack of adequate facilities result in high rates of under-diagnosis and incorrect treatment, both of which strongly influence the quality of life and lifespan of PWH.

The Hemophilia Federation of India (HFI) established in 1982 by families of PWH and other members of the medical and lay communities has 65 chapters across the country [5]. Diverging from what is done in the developed world, HFI provides factors free of cost or at subsidized rates, in addition to offering disease awareness, education, and psychosocial support. Following recent public interest litigations, however, states such as Delhi and Uttar Pradesh are providing hemophilia treatment free of cost [5]. As more states in India start providing free factor concentrates, it is expected that HFI will soon be able to focus on functioning as a research-oriented support group, psychosocial support group, patient registry resource database, and public awareness provider [5].

Burden of Inhibitors

Management of hemophilia A or B is based on the lifelong replacement of coagulation proteins. Today, the most feared complication of this therapy is the development of inhibitors that neutralize the replacement proteins (clotting factors) [8]. It is known that the risk of developing inhibitors is greatest for previously untreated patients (PUPs) with severe hemophilia A; however, hemophilia B patients can also develop inhibitors [9].

In one prevalence study conducted in Turkey [10], the authors found that the prevalence of inhibitors was 27%; however, since 17% were transient inhibitors, 10% was then considered as the final prevalence rate. Interestingly, in this study, inhibitors were detected in severe (41%) as well as in moderate hemophilia patients (33%). PUPs showed a higher rate of inhibitor development than previously treated patients (PTPs) [10].

McMillan et al. (1988) [11] prospectively described the epidemiological, clinical, and laboratory characteristics of 31 patients who developed inhibitors; these were identified from amongst 1,306 patients entering the study with an incidence of inhibitors as 8/1,000 patient-years of observation. Patients younger than 20 years were the most

affected and 94% of them had factor VIII: C levels ≤ 0.03 U/ml.

In a recent prevalence study among Chinese hemophilia A patients treated only with plasma-derived FVIII (pd-FVIII), cryoprecipitate, or fresh frozen plasma (FFP), the overall prevalence of inhibitors was 3.9% and the prevalence of severe hemophilia was 4.3% [12].

The prevalence of inhibitors in India is estimated to be 8.2–13% [13, 14]. During a 5 year follow up, 23 of 283 severe hemophilia patients were investigated for the presence of inhibitors before surgery or because of a suboptimal response to factor replacement therapy [15]. Nine patients were positive for inhibitors, and no transient cases were found in that cohort. Most of the patients received cryoprecipitate as replacement therapy before inhibitor diagnosis. After inhibitor diagnosis, they were managed with plasma-derived activated prothrombin complex concentrate (aPCC; FEIBA®; Baxter Bioscience, Vienna, Austria) or highly purified factor IX concentrates. The age of developing inhibitors among those patients was higher when compared to that reported by Western studies, most likely due to late exposure to factor replacement [15]. Ghosh et al. (2002) [16] described a case series of 35 patients, out of whom six developed inhibitors postoperatively. Patients were managed with aPCC and EACA. The latter had a hemostatic effect in three patients [16].

Unfortunately, there is no prospective study assessing inhibitors in PUPs in India; hence, the incidence of inhibitor development is still not known. Therefore, further epidemiological studies are required.

The cause of inhibitor development is multifactorial, and it is expected that patients will develop inhibitors within 10–15 exposure days, reaching a plateau after 50–75 exposure days [17]. Genetic factors have been associated with a higher risk of inhibitor development. Patients with large deletions, nonsense mutations, and intron 22 inversions have a seven to tenfold higher risk of inhibitor development [18]. Non-genetic risk factors have been extensively studied; however, data is lacking about proper assessment and quantification of risks. It seems that young age and the reason for the first infusion along with intensity of treatment could be important risk factors for inhibitor development [19]. Ghosh and Shetty (2009) [20] in a comprehensive review on the risk factors and immune response related to inhibitor development in congenital cases as well as in acquired hemophilia cases, highlighted the importance of modifiable factors for predicting and perhaps preventing the formation of inhibitors in hemophilia patients. Recent studies have reported a 60% reduction in the risk for inhibitor development in patients on prophylaxis compared to those on on-demand treatment [18–21]; however, further studies are required.

Diagnosis of Inhibitors

Diagnosing inhibitors, which are usually immunoglobulins (Ig) of the IgG class, demands specialized laboratories and expertise [14, 21, 22]. Each hemophilia treatment center should have its own protocol for the detection of inhibitors, and this protocol should involve systematic assessment, regardless of whether it is based on the number of exposure days, conducted before any surgical procedure, or in if it is conducted in case there is no response to regular factor replacement therapy [14].

Inhibitors can be assessed by an activated partial thromboplastin time (a-PTT)-based screening test, called the plasma-mixing test. Mixing studies are useful for detecting any interfering substance that prolongs the a-PTT in a mixture of patient and normal plasma after incubation at 37°C [21–23]. This test has been described elsewhere [21–23], and it is not in the scope of this review. Immunological assays should be avoided because they cannot assess inhibitor activity [23].

A definitive diagnosis is made by quantifying the inhibitors through the Bethesda assay or the Nijmegen-modified Bethesda assay [22–24]. One Bethesda unit (BU) is defined as the amount of inhibitor that results in 50% residual FVIII activity [25]. Either assay requires an experienced technician and a well-equipped laboratory. Both the methods are based on the principle of measuring the inactivation of factor VIII during a fixed incubation time and quantifying the activity of the remaining FVIII [24, 25]. Equal volumes of the patient plasma sample and an FVIII source (normal pool plasma in the Bethesda assay and imidazole-buffered normal pool plasma in the Nijmegen assay) are incubated for 2 h at 37°C, following which the activity of the remaining FVIII is measured by means of an FVIII activity method [24, 25]. The Nijmegen method seems to be more specific with less false positive results compared to the classical Bethesda method. Inter- and intra-laboratory variability play an important role as far as the quality of results is concerned. These assays should be standardized and optimized if their sensitivity and specificity are to improve [2].

Current Principles in the Management of Bleeding in Hemophilia with Inhibitors

The management of PWH and inhibitors comprises several approaches involving prompt treatment of bleeding episodes, managing its complications, preventing bleeds, and conserving and restoring joint function [9]. The ultimate goal of treating PWH and inhibitors is to permanently eradicate inhibitors via immune tolerance therapy (ITT), and the same therapy has been indicated for high-responder

patients in developed countries [26]. However, ITT is still not feasible in most centers in India because of prohibitive cost and logistics constraints [14].

Because of the different approaches available, patients should be classified according to their inhibitor titers (low <5 BU and high ≥ 5 BU) or historically according to their response level (low responder <5 BU and high responder ≥ 5 BU). Low titers or low response patients could be managed with higher doses of factor concentrates to overcome inhibitor levels [14] during mild to moderate bleeds. On-demand therapy with bypassing agents is the first option for high titer or high response patients. The two bypassing agents in the market are recombinant activated factor VII (rFVIIa; NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark) and aPCC [9]. The recommended dose of aPCC is 50–100 U/kg every 8–12 h. It is generally well-tolerated, with its efficacy rate varying from 60 to 80% [27, 28]. The use of human proteins during its manufacturing process, the large volume of infusion, and the risk of anamnestic response are some disadvantages for aPCC [29, 30]. aPCC has also an upper limit of 100 U/kg per dose and 200 U/kg per day, regardless of hemostatic response [30].

Because of its recombinant safety and lack of anamnestic response risk, rFVIIa could be recommended as a first-line therapy [31]. A standard dose of 90 $\mu\text{g/kg}$ every 2–3 h, three doses, has shown an effective response of 92% in mild and moderate bleeds [32, 33]. Recently, two randomized studies compared the standard dose of rFVIIa with a single-dose regimen of 270 $\mu\text{g/kg}$, and both regimens were considered efficient and safe for mild and moderate bleeds and more efficient than aPCC [34, 35]. In one study, rescue medication at 9 h was required for 36.4% of aPCC patients, whereas it was required for only 8.3% of rFVIIa patients who received a single dose ($P = 0.032$) [35].

In a recent study conducted in Turkey, the authors assessed the relationship between time to initiation of rFVIIa and total cost, number of doses administered, and time to bleeding resolution in mild to moderate bleeding episodes. They found that rFVIIa if initiated as soon as possible after the onset of bleeding could minimize costs and optimize outcomes [36]. Elective orthopedic surgical procedures have also been made possible for PWH with inhibitors [37]. Moreover, there is a promising role for rFVIIa as a prophylactic agent aiming at joint conservation and functionality with consequent improvement in quality of life [38].

Hemophilia Care in Uttar Pradesh: Changing Scenario

Availability of free factors in some states of our country is a refreshing and welcome change for PWH. We will now

discuss the experience of a hemophilia centre in Uttar Pradesh in the context of the availability of free factor concentrates. The department of Medical Genetics at Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow, has been providing holistic care to PWH and their families for the last 20 years. This included diagnosis, treatment of joint bleeds and serious life-threatening bleeds, patient education, genetic counseling, and prenatal diagnosis.

The use of factor concentrates was less than 5% for inpatients because treatment facilities for PWH were practically non-existent. PWH from all over Uttar Pradesh and surrounding states have been coming to SGPGIMS, Lucknow. Severe joint bleeds, intramuscular bleeds, oral bleeds, injuries, and serious bleeds (intraperitoneal, gastrointestinal, and intracranial bleeds) were the most frequent reasons for visits. Blood products were the mainstay of treatment, and patients were managed with lower levels of factors than the conventional doses described in textbooks. Elective surgeries were out of the question, but emergency surgeries were carried out, especially for intracranial bleeds with the combined support of factor concentrates and wet products. The number of patients treated per year continued to increase and varied between 60 and 100 per year. In a period of about 18–19 years, two patients who developed inhibitors were identified. There were various challenges, including the development of inhibitors and misdiagnosed cases. Bypassing agents were not systematically available, and the bleeding episodes were managed with aPCC and adjunct measures.

At SGPGIMS, genetic counseling and prenatal diagnosis for hemophilia has been an important component of hemophilia management [39]. Information regarding screening of probable carriers and prenatal diagnosis is provided to all families. Meetings with female members of hemophilia families are held to educate them about the genetic aspects of the disease and to decrease the stigma associated with carrier females [40]. Seventy-seven cases have been diagnosed prenatally during last 10 years.

In June 2009, the Government of Uttar Pradesh made anti-hemophilic factors available in a few centers, including SGPGIMS, Lucknow. Consequently, the level of hemophilia care has improved considerably in recent times. The treatment has been life-saving for some and decreased pain for many. It has also improved the quality of life, especially of those with good physiotherapy results. This is a milestone in hemophilia management in Uttar Pradesh and has been a period of great satisfaction and a learning experience for treating doctors. In 9 months, approximately 200 patients made more than 2000 visits to SGPGIMS, Lucknow, for bleeding episodes of varying severity. Emergency and elective surgeries were performed. Short-term prophylactic factor infusions were given to some

patients who were undergoing physiotherapy and to wheelchair-bound patients who achieved mobilization. Two previously diagnosed and one newly diagnosed case of hemophilia with inhibitors was treated successfully with rFVIIa and tranexamic acid. Amongst the current 200 PWH, three have developed inhibitors. Inhibitors were suspected in two additional cases of hemophilia A because the patients showed no response to factor VIII infusions. However, they turned to be negative for inhibitors but had deficiency of factor IX rather than VIII as reported in the past. Our laboratory has been able to provide better diagnosis assessment, including inhibitor diagnosis as compared to previous years. Recently, the Transfusion Department of SGPGIMS conducted a hemophilia workshop and laboratory training program for hemophilia diagnosis with participants from several institutions across Uttar Pradesh. Nevertheless, systematic inhibitor screening of all patients has not yet been done and the magnitude of the problem of inhibitors remains unclear. Since patients are being exposed to factor replacement in a more regular way, there is an urgent need for establishing a protocol for inhibitor screening. Presently, we conduct screening only before surgery or when there is no response to factor replacement therapy.

Overall, it has been a rewarding experience for the patients and treating doctors alike.

Nevertheless, despite these positives, hemophilia treatment is far from optimum. Efforts to improve management facilities, increase awareness, reinforce knowledge, and improve coordination are ongoing. We emphasize the need for more work in the following directions in order to improve hemophilia care at SGPGIMS, Lucknow: (1) systematic screening for inhibitors; (2) identification of the current number and demographics of PWH; (3) provision for comprehensive hemophilia treatment, including physiotherapy, patient education, orthopedic treatment under one roof, and (4) early treatment and prophylaxis.

Conclusion

In India, because patients are administered factor replacement erratically, with frequent switching of brands, there is always a chance that confounders will cloud our understanding of inhibitor development in PWH; this is an additional challenge for the comprehensive care of PWH.

As hemophilia care improves, centers should aim to gather professionals who can provide comprehensive care and develop laboratory facilities for the detection and periodic screening of inhibitors. If the government is willing to provide support in the form of free anti-hemophilic factors and bypassing agents, treating doctors must plan the budget and treatment facilities and provide good

diagnostics and comprehensive care. While treating PWH, providing safe products should be of prime importance. The availability of bypass agents such as rFVIIa in India should improve, given that several clinical studies have established the safety and efficacy of this bypassing agent in PWH with inhibitors.

The treating doctor not only has to be knowledgeable about the management of hemophilia with or without inhibitors but should also be willing to take up the important role of policy maker and adviser and help the government in planning and organizing hemophilia care in India. As we move forward, the role of HFI, medical associations, and governments need to be well-defined, and these institutions should have the common objective of promoting better care and a near-normal life for PWH.

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