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Prevalence of Factor VIII Inhibitors, Transfusion-Transmitted Infections, and Bypass Agent Requirement in Hemophilia: A Hospital-Based Cross-Sectional Study

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Abstract

Background: Hemophilia is an inherited bleeding disorder caused by deficiency or dysfunction of coagulation factors, most commonly factor VIII (Hemophilia A) or factor IX (Hemophilia B). The disease is inherited in an X-linked recessive pattern and predominantly affects males. Recurrent bleeding episodes, particularly into joints and muscles, lead to chronic complications such as hemophilic arthropathy and disability. Despite advances in replacement therapy, major challenges in hemophilia management include the development of inhibitors against clotting factors and the risk of transfusion-transmitted infections (TTIs) such as hepatitis B, hepatitis C, and HIV. Patients who develop inhibitors often require bypassing agents for effective bleeding control. ***Aim:*** To determine the prevalence of factor VIII inhibitors, transfusion-transmitted infections, and the use of bypassing agents among patients with hemophilia treated at a tertiary care center. ***Materials and Methods:*** A hospital-based cross-sectional observational study was conducted in the Department of Medicine at SSG Hospital, Vadodara over a period of six months. A total of 75 adult patients diagnosed with Hemophilia A or Hemophilia B were included. Clinical data were collected using a predesigned questionnaire. Laboratory investigations included complete blood count, coagulation profile, factor assays, and screening for transfusion-transmitted infections. Descriptive statistical analysis was performed using percentages, means, and standard deviations. ***Results:*** Among the 75 patients studied, Hemophilia A was the predominant type, accounting for 66 cases (88%), while Hemophilia B was observed in 9 cases (12%). Severe hemophilia was the most common presentation, affecting 57 (86%) of Hemophilia A patients. Factor VIII inhibitors were detected in 27 patients (36%), and all inhibitor-positive cases occurred among individuals with severe hemophilia. Screening for transfusion-transmitted infections revealed HBsAg positivity in 4 patients (5.3%), HCV positivity in 2 patients (2.6%), and HIV positivity in 1 patient (1.3%). Among patients with high-titer inhibitors, Emicizumab was the most commonly used bypassing therapy (62%), followed by FEIBA (23%) and recombinant activated factor VII (15%). ***Conclusion:*** Hemophilia A was the most prevalent form of hemophilia, with severe disease predominating. Inhibitor development remains a major complication, particularly among patients with severe hemophilia. Although the prevalence of transfusion-transmitted infections was relatively low, continued emphasis on safe transfusion practices and improved access to recombinant therapies is essential for optimal hemophilia management.

Keywords: Hemophilia, Factor VIII inhibitors, Transfusion-transmitted infections, Bypassing agents, Hemophilia A, Emicizumab.

INTRODUCTION

Hemophilia is a hereditary bleeding disorder characterized by deficiency or dysfunction of coagulation factors required for normal hemostasis. Males are mostly affected by the condition, which is transmitted in an X-linked recessive form. Females are often carriers. [1] Factor VIII deficiency causes hemophilia A, while factor B deficiency causes hemophilia B. IX. About 80–85% of all instances of hemophilia are caused by hemophilia A, whereas 15–20% are caused by hemophilia B. [2] Hemophilia A is thought to affect 1 in 5,000–10,000 male births worldwide, whereas Hemophilia B affects around 1 in 30,000 male births. Hemophilia still places a heavy burden on patients despite breakthroughs in diagnosis and treatment because of recurring bleeding episodes, long-term joint damage, and treatment-related problems. [3]

The development of inhibitors against clotting factors, especially factor VIII, is one of the most dangerous side effects of managing hemophilia. These inhibitors are neutralizing antibodies that lessen replacement therapy's

efficacy and make controlling bleeding episodes challenging. Inhibitors are developed in around 30% of people with severe hemophilia A, but the frequency is lower in patients with moderate and mild hemophilia A. [4]

The possibility of transfusion-transmitted diseases (TTIs) including HIV, hepatitis B, and hepatitis C is another significant worry. In the past, hemophiliacs who used plasma-derived clotting factors had extensive viral transmission. Recombinant factor concentrates and better screening have lowered this danger, but TTIs are still a major issue in underdeveloped nations where access to quality blood products may be restricted.

Hemophilia frequently manifests as bleeding in the muscles and joints. The most common symptom is hemarthrosis, or bleeding into joints, which can result in hemophilic arthropathy, joint abnormalities, and chronic synovitis. Mobility and quality of life are severely hampered by these issues.[5]

Replacement treatment with insufficient clotting factors is the mainstay of hemophilia management. However, traditional factor replacement is no longer effective in individuals who develop inhibitors. In these situations, bleeding is managed using bypassing medicines such activated prothrombin complex concentrates (APCC) and recombinant activated factor VII (rFVIIa). [6] Understanding the incidence of inhibitor formation, transfusion-related infections, and bypassing treatment in hemophilia patients is crucial for improving management approaches because of their clinical significance. The goal of the current study was to assess these variables in hemophiliac patients who were hospitalized to a tertiary care facility.

MATERIALS AND METHODS

Study Design: This study was conducted as a hospital-based observational cross-sectional study.

Study Setting: The study was carried out in the Department of Medicine at SSG Hospital, Vadodara.

Study Duration: The study was conducted over a 6-month period.

Sample Size: A total of 75 patients diagnosed with hemophilia were included in the study.

Inclusion Criteria

- Patients aged >18 years
- Diagnosed cases of Hemophilia A or Hemophilia B
- Patients who provided informed consent

Exclusion Criteria

- Patients who refused consent for participation

Data Collection

A predesigned questionnaire was used to collect patient data. Detailed history was obtained regarding:

- Demographic information
- Family history of bleeding disorders
- History of blood transfusion
- Clinical manifestations
- Frequency of bleeding episodes
- Need for factor replacement therapy

Physical examination and systemic evaluation were performed for all patients.

Laboratory Investigations

All patients underwent the following investigations:

- Complete blood count
- Peripheral smear
- Coagulation profile
- Factor assays
- Screening for transfusion-transmitted infections
- Radiological investigations when required

Statistical Analysis

Data were analyzed using descriptive statistics, including percentages, means, and standard deviations.

RESULTS

Table 1: Distribution of Patients According to Type of Hemophilia (n = 75)

Type of Hemophilia	Number of Patients	Percentage (%)
Hemophilia A	66	88%
Hemophilia B	9	12%
Total	75	100%

Table 1 shows the distribution of patients according to the type of hemophilia among the study population. Out of the total 75 patients included in the study, 66 patients (88%) were diagnosed with Hemophilia A, whereas 9 patients (12%) had Hemophilia B. This indicates that Hemophilia A was the predominant type observed among the study participants.

Table 2 illustrates the severity distribution among patients with Hemophilia A. Among the 66 Hemophilia A patients, the majority 57 patients (86%) had severe hemophilia, characterized by factor levels below 1%. Moderate hemophilia (1–5%) was observed in 8 patients (12%), while only 1 patient (2%) had mild hemophilia (5–30%). These findings demonstrate that severe hemophilia constituted the largest proportion of cases in the study population.

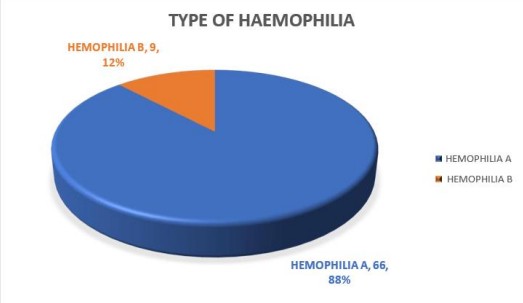

Figure 1: Type of Hemophilia

Table 2: Severity of Hemophilia A (n = 66)

Severity	Number of Patients	Percentage (%)
Mild (5–30%)	1	2%
Moderate (1–5%)	8	12%
Severe (<1%)	57	86%
Total	66	100%

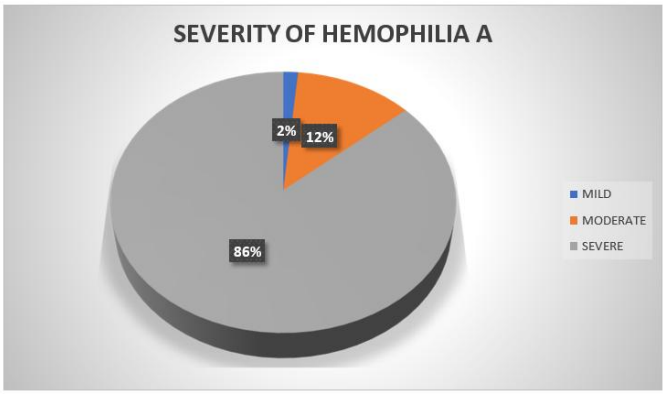

Figure 2: Severity of Hemophilia

Table 3: Inhibitor Development Among Hemophilia Patients (n = 75)

Inhibitor Development	Number of Patients	Percentage (%)
Present	27	36%
Absent	48	64%
Total	75	100%

Table 3 presents the prevalence of inhibitor development among the hemophilia patients included in the study. Out of the 75 patients evaluated, 27 patients (36%) were found to have factor inhibitors, whereas 48 patients (64%) did not show inhibitor development. Notably, inhibitor positivity was observed exclusively among patients with severe hemophilia, suggesting a strong association between disease severity and inhibitor formation

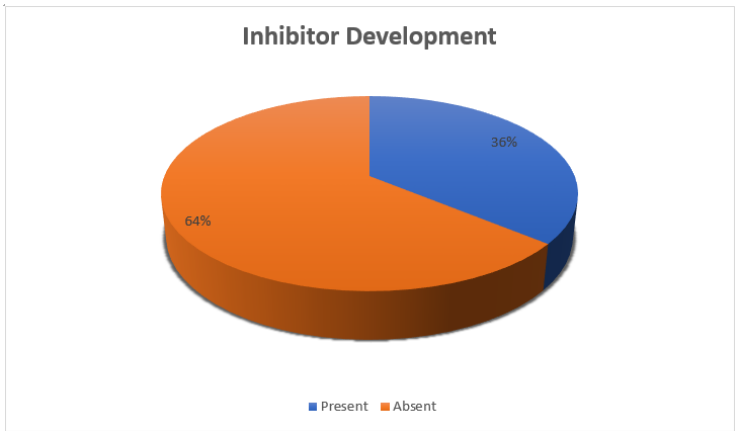

Figure 3: Inhibitor Development Among Hemophilia Patients

Table 4: Transfusion-Transmitted Infections in Hemophilia Patients (n = 75)

Infection	Present	Absent	Percentage (%)
HBsAg	4	71	5.3%
HCV	2	73	2.6%
HIV	1	74	1.3%

Table 4 describes the prevalence of transfusion-transmitted infections among the study participants. Screening for viral infections revealed that 4 patients (5.3%) were positive for hepatitis B surface antigen (HBsAg), 2 patients (2.6%) were positive for hepatitis C virus (HCV), and 1 patient (1.3%) tested positive for HIV infection. The remaining patients were negative for these infections. These findings indicate that although the prevalence of transfusion-transmitted infections was relatively low, a small proportion of patients remained affected.

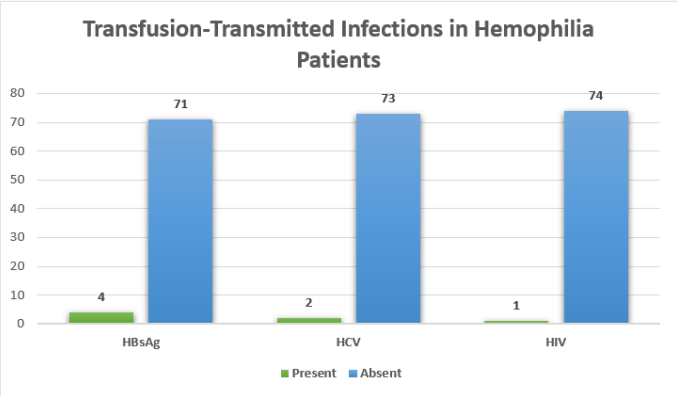

Figure 4: Transfusion-Transmitted Infections in Hemophilia Patients

Table 5: Use of Bypassing Agents in High Responder Inhibitor Patients (n = 13)

BYPASSING AGENT	NO. OF PATIENTS	PERCENTAGE
FEIBA	3	23%
NOVO-7	2	15%
EMICIZUMAB	8	62%
TOTAL	13	100%

Table 5 summarizes the use of bypassing agents among patients with high-responder inhibitors. Among the 13 high-responder inhibitor patients, Emicizumab was the most frequently used bypassing therapy, administered in 8 patients (62%). FEIBA was used in 3 patients (23%), while NovoSeven (recombinant activated factor VII) was used in 2 patients (15%). These results highlight the increasing use of newer therapeutic agents such as Emicizumab in the management of hemophilia patients with inhibitors.

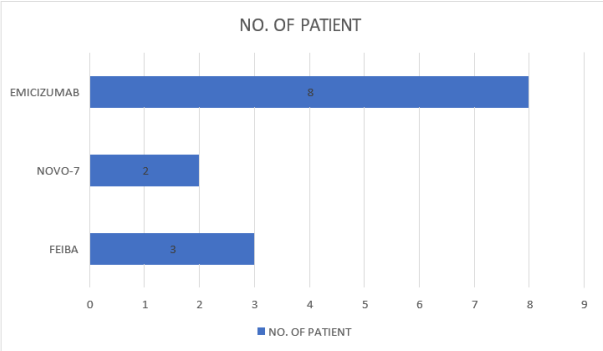

Figure 5: BYPASSING AGENT

DISCUSSION

The present hospital-based cross-sectional study evaluated the prevalence of factor VIII inhibitors, transfusion-transmitted infections (TTIs), and the requirement of bypassing agents among hemophilia patients admitted to SSG Hospital, Vadodara. Hemophilia remains one of the most common inherited bleeding disorders worldwide, characterized by deficiency of coagulation factors VIII or IX, leading to recurrent bleeding episodes and significant morbidity if

untreated. Hemophilia A accounts for the majority of cases globally due to deficiency of factor VIII [7].

Hemophilia A predominated in the current research, with 88% of patients having hemophilia A and 12% having hemophilia B. Previous research carried out in India and other locations have revealed similar results. Mishra & al. found hemophilia A in 88.3% and hemophilia B in 11.7% of cases, whereas Agarwal et al. found hemophilia A in 73.6% and hemophilia B in 21.4% of patients. Similarly, 82% of patients had hemophilia A, according to Parthiban et al. Hemophilia A is still the most common subtype in many demographics and healthcare environments, as these studies repeatedly show [8,9,10].

Additionally, severe hemophilia was the most common clinical presentation, especially in patients with hemophilia A, according to the current study. Just 12% and 2% of the 66 hemophilia A patients had moderate and mild illness, respectively, whereas 86% of them had severe disease. Mishra et al. observed similar findings, with severe hemophilia accounting for 80.5% of cases. Additionally, around two-thirds of patients had severe illness, according to Parthiban et al. Factor levels below 1% indicate severe hemophilia, which is commonly linked to spontaneous bleeding episodes and a higher risk of complications such hemarthrosis and inhibitor development [9,10].

The emergence of inhibitors to factor VIII replacement therapy is one of the main side effects of hemophilia treatment. Inhibitors were found in 36% of the patients in the current investigation, and all inhibitor-positive instances were individuals with severe hemophilia. This result is in line with other studies showing that people with severe hemophilia are more likely to produce inhibitors. According to epidemiological research, 20–30% of people with severe hemophilia A develop inhibitors, while the frequency is much lower in patients with mild and moderate hemophilia [11]. Inhibitor formation was further verified in about 32% of patients with severe hemophilia by the RODIN research, underscoring the need of early inhibitor discovery and surveillance [12].

Only two of the 27 inhibitor-positive individuals in this research had severe hemophilia B, whereas 25 had severe hemophilia A. This suggests that inhibitor formation is far more prevalent in hemophilia A. According to earlier research, the occurrence of inhibitors in hemophilia A varies from 20 to 33%, depending on treatment exposure and hereditary variables, whereas the prevalence in hemophilia B is quite uncommon, ranging from 1 to 5% [11,13].

52% of hemophilia A patients using inhibitors were poor responders (<5 BU/ml), whereas 48% were high responders (>5 BU/ml), according to further examination of inhibitor titers. Because they neutralize infused factor VIII and make traditional replacement treatment ineffective, high-titer inhibitors have more therapeutic significance. Alternative treatment strategies, such bypassing agents, are necessary for the management of these individuals. For determining inhibitor levels in hemophilia patients, the Nijmegen-Bethesda test is presently regarded as the gold standard laboratory technique [14].

The relationship between cumulative exposure days and inhibitor development was also assessed in this investigation. Patients who had more than 30 exposure days were shown to be far more likely to acquire inhibitors. Similar findings have been shown in earlier research, where a significant risk factor for inhibitor development has been found to be repetitive exposure to clotting factor concentrates. Gouw et al. showed that early exposure to factor VIII products and treatment intensity had a substantial impact on the development of inhibitors in hemophilia patients [12].

Assessing the frequency of transfusion-transmitted infections among hemophilia patients was one of the study's other key goals. Of the 75 individuals that were screened, 5.3% had HBsAg, 2.6% had HCV, and 1.3% had HIV. Even though these numbers are lower than those from earlier research, they nonetheless demonstrate the danger of repeatedly transfusing blood products. Previous research by Ghosh et al. found that hemophilia patients receiving plasma-derived products had a noticeably greater frequency of viral infections. However, the prevalence of transfusion-transmitted illnesses has dramatically decreased in recent years due to advancements in donor screening, nucleic acid testing, and the growing availability of recombinant factor concentrates [15,16].

In order to establish adequate hemostasis, bypassing medications are frequently used in the management of hemophilia patients on inhibitors. The most common bypassing treatment in the current investigation was emicizumab (62%), which was followed by FEIBA (23%) and recombinant activated factor VII (NovoSeven) in 15% of patients. Emicizumab is a bispecific monoclonal antibody that restores coagulation by bridging active factor IX and factor X in a manner similar to that of factor VIII. Emicizumab dramatically lowers bleeding episodes and enhances quality of life in hemophilia A patients taking inhibitors, according to recent clinical studies [17].

Overall, the results of this study demonstrate that developing inhibitors is still a major obstacle to managing hemophilia, especially in individuals with severe illness. Even though better screening methods have reduced the incidence of transfusion-transmitted illnesses, ongoing attention to detail and the use of safer treatment approaches are still crucial. Improving access to recombinant factor therapy, encouraging early preventive treatment, and growing the number of hemophilia treatment facilities are essential measures for

enhancing clinical results and quality of life for hemophilia patients, particularly in environments with limited resources.

CONCLUSION

A genetic bleeding illness, hemophilia still presents serious clinical difficulties, especially in underdeveloped nations. According to the current study, hemophilia A was the most prevalent kind, and the most common clinical presentation was severe hemophilia. There was a substantial correlation between the severity of the illness and the formation of inhibitors, as evidenced by the 36% frequency of factor VIII inhibitors and the fact that all inhibitor-positive instances were found in individuals with severe hemophilia. A limited percentage of patients had transfusion-transmitted diseases, such as HIV (1.3%), HBsAg (5.3%), and HCV (2.6%). The use of more recent medications, including emicizumab, demonstrates improvements in the treatment of hemophilia. Improving results requires bolstering access to contemporary medicines, safe transfusion procedures, and early diagnosis.

LIMITATIONS OF THE STUDY

1. The study was conducted at a **single tertiary care center**, which may limit the generalizability of the findings to the broader population.
2. The **sample size was relatively small (75 patients)**, which may influence the observed prevalence rates of inhibitors and transfusion-transmitted infections.
3. The study had a **cross-sectional design**, preventing long-term follow-up of patients and evaluation of inhibitor development over time.
4. Genetic analysis for identifying mutations associated with inhibitor development was not performed.

Socioeconomic and treatment-related factors influencing access to recombinant therapy could not be comprehensively assessed.

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