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Prevalence of inhibitors in patients with hemophilia treated with factor viii or ix transfusion

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Abstract
Aim and Objectives: It is a study of prevalence of inhibitors in patients with severe hemophilia using Bethesda assay and to correlate the prevalence of inhibitors with degree of factor exposure.
Methodology: This was an observational study. 50 patients with severe hemophilia were selected based on their factor levels. Among them, Hemophilia A contributed to 36 patients, whereas 14 patients had Hemophilia B. Inhibitor assay was done using Bethesda assay. Inhibitor development was analyzed by comparing the various factors which influence the development of inhibitors.
Results: Among the patients with severe hemophilia A, 31% had inhibitors, of which 25% had high responding inhibitors and 6% had low responding inhibitors. Among the severe hemophilia B patients, 7% had inhibitors. Small sample size may be a reason for the high prevalence noted in our study. The Mean age of patients with inhibitors and without inhibitors was 19.33 years and 23.63years respectively. Patients with more than 30 cumulative exposure days to factor VIII or factor IX had 53% more risk of developing inhibitors.
Conclusion: Patients who were diagnosed earlier and those with family history of inhibitors had significantly higher risk of developing inhibitors during the course of treatment. Patients with inhibitors also had a high bleeding score.

Keywords: hemophilia, factor VIII, Bethesda assay, factor IX, inhibitors

Introduction
Deficiency or absence of factor VIII or factor IX causes hemophilia A and hemophilia B respectively. According to the level of factor VIII hemophilia is classified into mild, moderate and severe forms. In the severe and moderate forms, the disease is characterized by spontaneous or trauma related bleeding into the large joints or muscles [1]. In mild disease the patient experiences infrequent Bleeding especially after trauma. If the Factor VIII or IX level is >25% the disease is diagnosed only during routine preoperative Screening tests or after major trauma. Recent problem in treating patients with hemophilia is development of alloantibodies against factor VIII or IX, also known as inhibitors [2]. This should be suspected if the patient is not responding to replacement of missing factor at therapeutic doses. Prevalence rate is 5-10% of all cases and 20% of severe hemophilia A Patients. Only 3-5% of hemophilia B patients detected to have inhibitors [3]. Here we studied the prevalence of inhibitors in persons with severe hemophilia who have had exposures to FVIII or FIX concentrates.

Materials and Methods
Study design: Observational study
Patient selection: 50 patients admitted in Coimbatore Medical College hospital with severe hemophilia during the year 2013- 14.
Inclusion criteria: Patients admitted with severe hemophilia based on factor level.
Exclusion criteria:
- Drug intake (penicillin, phenytoin, interferon).
- Known case of systemic lupus erythematosus, Rheumatoid arthritis.
- Patients with acquired hemophilia.
- Hemophilia patients not willing to participate in this study.

Techniques
History and Examination
All patients with hemophilia willing to participate in the study were assessed as per the criteria submitted to institutional ethics committee. Patients with severe hemophilia were taken based on factor level from the patient records. Thorough history was taken about the number of exposure to factor concentrates and blood products. Family history was obtained in detail.
The factor levels are measured by Bethesda assay. Bleeding score was based on the score set by the World Federation of Hemophilia. Bleeding score was used to assess severity of the disease. Informed consent was obtained from all patients before starting the study.

Statistical Methods
Statistical analysis was performed using SPSS version 19.0. Normal data were measured using mean and standard deviation to correlate various clinical variables Pearson correlation co-efficient with single tail analysis was done.

Results
Among the patients studied 72 percent had hemophilia A and the remaining 28 Percent had hemophilia B. Three patients with severe disease had family History of inhibitors. Among the patients with severe hemophilia A, 31% had inhibitors, of which 25% had high responding inhibitors and 6% had low responding inhibitors. Among the severe hemophilia B patients, 7% had inhibitors. Small sample size may be a reason for the high prevalence noted in our study.

The Mean age of patients with inhibitors and without inhibitors was 19.33 years and 23.63 years respectively. Patients with more than 30 cumulative exposure days to factor VIII or factor IX had 53% more risk of developing inhibitors. Patients who were diagnosed earlier and those with family history of inhibitors had significantly higher risk of developing inhibitors during the course of treatment. Patients with inhibitors also had a high bleeding score. Inhibitor development was compared with age at the time of diagnosis of hemophilia. Patients with early age at the time of diagnosis had more chance for development of inhibitors and vice versa. The mean age at the time of diagnosis of patients with inhibitor is 7.92 yrs and without inhibitor is 25.32 yrs. Inhibitor development was compared with family history of inhibitors. Patients with family history of inhibitors had very high risk for development of inhibitors. This association was statistically more significant with P value of 0.000.

Discussion

Deficiency or absence of factor VIII or factor IX causes hemophilia A and B respectively. Recent problem in treating patients with hemophilia is the development of alloantibodies against factor VIII or IX, also known as inhibitors. This should be suspected if the patient is not responding to replacement of missing factor at therapeutic doses. According to various studies done all over the world around 25-38 percent of severe hemophilia a patients have inhibitors. In our study the prevalence of inhibitors in patients with severe hemophilia A was 31%.Among them 25% had high responding inhibitors and 6% had low responding inhibitors. In this study the prevalence of inhibitors in patients with severe hemophilia B was 7%. Exposure to blood products like cryoprecipitate, Fresh Frozen Plasma and whole blood had no significant correlation with inhibitor development. In our study, patients with family history of inhibitors had very high risk for inhibitor development. Various studies have proven significant statistical correlation of family history with inhibitors. This may be further confirmed by doing the study in larger group of patients.

Conclusion

Results from the study showed that inhibitor development were more common in severe hemophilia A than hemophilia B. Patients with more number of cumulative exposure days, earlier age at the time of diagnosis and patients with family history of inhibitors had high risk for development of inhibitors when compared to others. So regular screening of patients with hemophilia is mandatory to reduce the economic burden, as well as to reduce the disability rate. This study can be further done with larger sample size to get more authentic proof.

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