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ORIGINAL ARTICLE

Effect of Prophylactic Management of Hemophilia on Bleeding Episodes

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Abstract Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) are the most common and serious congenital coagulation factor deficiencies with repeated hemarthroses leading to development of target joints. Continuous prophylaxis is regular infusion of factor concentrates at fixed dose at regular interval to prevent hemorrhages. The study was designed to assess the outcome of continuous prophylaxis in hemophilia on bleeding episodes. It was conducted from November, 2017 to April, 2018 in the Paediatrics Department of Midnapore Medical College, Paschim Medinipur, West Bengal on 33 boys from 4 to 18 years of age suffering from Hemophilia with frequent bleeding episodes. Prior to starting continuous prophylaxis all the patients' target joint(s) were assessed based on Gilbert Score and bleeding episodes in the last 6 months were assessed based on Annualized Bleeding Rate and ISTH-BAT Score. All the children were provided prophylaxis therapy with plasma derived Factor concentrate twice per week at a dose of 20 + − 2 IU/Kg. All bleeding episodes of the children during prophylaxis were recorded. Bleeding episodes showed significant improvement only in children who could sufficiently adhere to continuous prophylactic therapy. Continuous prophylaxis reduces bleeding episodes in Hemophilia in twice weekly protocol provided the patients sufficiently adhere to continuous prophylaxis regimen.

Keywords Hemarthrosis · Gilbert score · ISTH-BAT score · Prophylaxis

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Introduction

Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) are the most common and serious congenital coagulation factor deficiencies [1]. Their clinical manifestations are identical, with an increased tendency for musculoskeletal, soft tissue and mucocutaneous bleeding. Bleeding into other organs also occur [2]. Although bleeding may occur in any area of the body, the hallmark of hemophilic bleeding is hemarthrosis [1].

Repeated hemarthroses lead to the development of target joints, which are more prone to continuous bleeding and the development of chronic arthropathy. Target joint is defined as a single joint that has experienced three or more bleeds in a consecutive 3-month period [3]. Joint bleeding initially leads to independent adverse changes in both the synovial tissue and the articular cartilage. Both synovial inflammatory changes and cartilage damage affect each other [4].

According to their residual endogenous FVIII/FIX concentrations, individuals with a factor level < 1 IU/dL are classified as severe hemophiliacs and represent about half of diagnosed cases. Subjects with factor levels between 1–5 IU/dL and > 5 IU/dL have moderate and mild hemophilia, respectively. Although the bleeding phenotype may be rather heterogeneous, even in severe hemophiliacs, this classification reflects the severity of clinical symptoms, with spontaneous joint and muscle

bleeds being largely confined to patients with severe hemophilia [5].

Concentrate infusions when hemorrhages occur typically in joint and muscles (on-demand treatment) is able to resolve bleeding, but does not prevent the progressive joint deterioration leading to crippling hemophilic arthropathy. Therefore, primary prophylaxis, i.e., regular infusion of concentrates started after the first joint bleed and/or before the age of 2 years, is now recognized as first-line treatment in children with severe hemophilia. Secondary prophylaxis, whenever started, aims to avoid (or delay) the progression of arthropathy and improve patient quality of life [6].

There are two prophylaxis protocols currently in use for which there is long-term data. The Malmo protocol recommends 25–40 IU/kg per dose administered three times a week for those with hemophilia A, and twice a week for those with hemophilia B. The Utrecht protocol recommends 15–30 IU/kg per dose administered three times a week for those with hemophilia A, and twice a week for those with hemophilia B [7].

Several hemophilia-specific scores are available to measure joint impairment and function, including activities and participation. Gilbert score is a physical examination score. It assesses joint health in patients with hemophilic arthropathy [8]. The ISTH-BAT (International Society on Thrombosis and Hemostasis-Bleeding Assessment Tool) was developed as a tool with which to accurately record bleeding symptoms in all hemorrhagic disorders and to aid diagnosis in patients referred with a possible bleeding disorder [9].

The aim of this study is to assess joint health and bleeding episodes in children suffering from hemophilia before and after introduction of secondary prophylactic therapy with factor concentrates.

Materials and Methods

The study was conducted on 33 boys of age ranging from 4 to 18 years who were members of Hemophilia Society, Kharagpur Chapter motivated to attend the Hemophilia Centre in the Paediatrics Department of Midnapore Medical College, Paschim Medinipur, West Bengal for primary prophylaxis therapy. Of the 33 children 30 had at least one target joint. All of them had their endogenous factor assay estimated at the time of diagnosis. All the children were tested negative for factor inhibitor both before and after the study. Out of the 33 children included in the study 19 were severely hemophilic and the rest were moderately Hemophilic.

Detailed history including age at first hemarthrosis, bleeding events leading to diagnosis of hemophilia, family history of bleeding disorders and average annual joint bleeds were taken. Prior to starting continuous prophylaxis of all the children their target joint(s) were assessed based on Gilbert Score. Annual joint bleeding rate was estimated by calculating the number of joint bleeds in last 1 year through history taking and documents of hospital admission for bleeding wherever available. We documented all bleeding episodes in the last 6 months and calculated their Annualized Bleeding Rate (ABR). Also we rated the bleeding episodes as per definitions of ISTH-BAT criteria and created a bleeding score.

All the children were provided prophylaxis therapy free of cost with human plasma derived lyophilized factor VIII or IX concentrate twice per week (on Mondays and Thursdays) at a dose of 20 ± 2 IU/Kg. In case of bleeding episodes they were admitted to the inpatient ward and managed according to standard protocol with factor concentrate, pain management application of ice and elevation of limb. We calculated the total number of weeks they received two prophylactic doses in last 6 months. We recorded all bleeding episodes during these 6 months. After 6 months of prophylaxis their ABR and bleeding score based on ISTH-BAT criteria were again calculated and compiled.

Statistical Methods

Data were analysed using Statistical Package for Social Sciences (version 23). Statistical analysis was performed using Student t test to establish the significance of difference between means of two dependent variables, Independent samples t test to establish the significance of difference between means of two independent variables and Spearman's correlation coefficient (rho) to find out correlation between two variables.

Significance was considered at p value less than 0.01.

Results

A total of 33 boys of age ranging from 4 to 18 years (mean = 10.8) were enrolled for the study. 31 of them were suffering from hemophilia A and 2 of them were patients of hemophilia B. 19 children were severely hemophilic (57.57%) and the rest were moderately hemophilic (42.42%). There was no case of mild hemophilia. No statistically significant difference was found between annual bleeding rate of severe and moderately hemophilic groups with p value of 0.99.

30 children (90.9%) had developed one or more target joint(s). Knee joint was found to be the most involved target joint (52.9%) followed by elbow joint (38.2%). There were only 2 cases of ankle joint (5.9%) and 1 case of shoulder joint (2.9%) involvement (Fig. 1).

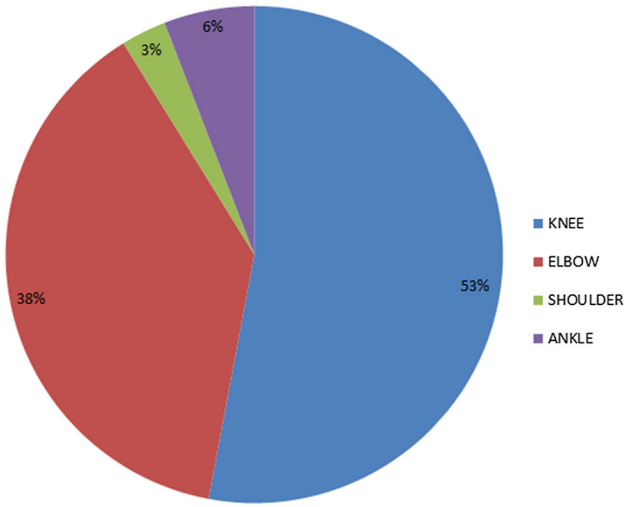

Fig. 1 Distribution of target joints

Age of first joint bleeding ranged from 1 to 7 years (mean = 3.4). Annual joint bleeding rate ranged from 3 to 12 episodes per year (median = 7, mode = 6). Gilbert score of target joints ranged from 4 to 14 (mean = 7.8, median = 8). No statistically significant correlation was found between percentage of endogenous factor activity and Gilbert score (rho = 0.07, p value = 0.69). A positive correlation was found between ages of the children with Gilbert score (rho = 0.56, p value = 0.001) which was statistically significant. No correlation was found between age of first onset of joint bleeding and Gilbert score (rho = − 0.23, p value = 0.23) which was statistically not significant. A positive correlation was found between annual joint bleeding rate and Gilbert score (rho = 0.52, p value = 0.003) which was statistically significant. We calculated the estimated total number of joint bleeds in each child using a formula: [(Age of child-Age of onset of first joint bleed) * Annual joint bleeding rate]. A strong positive correlation was found between estimated total joint bleeds in the children and Gilbert score (Fig. 2). Spearman correlation coefficient was 0.77 with p value of 0.000001 which was statistically highly significant.

Total number of weeks of prophylactic doses received by each child ranged from 10 to 22. (mean = 14.8, median = 14). For better analysis we divided the children in two groups based on the total number of weeks of prophylactic doses received: Group A (received prophylaxis for $<$ 15 weeks) and Group B (received prophylaxis for $\geq$ 15 weeks). Gilbert score before prophylaxis ranged from 4 to 14 (mean = 7.8, Median = 8, Mode = 4).

Annualized Bleeding Score (ABR) before prophylaxis ranged from 4 to 12 (Mean = 8.3, Median = 8). ABR during prophylaxis ranged from 4 to 12 (Mean = 7.21, Median = 8). ABR before and after 6 months of prophylaxis was compared using paired student t test separately in each group of patients. No significant improvement of ABR was found in Group A patients (p value = 0.87) which was statistically insignificant. However improvement of ABR was found in Group B patients (p value = 0.007) which was statistically significant (Fig. 3).

ISTH-BAT based bleeding score for 6 months before prophylaxis ranged from 6 to 18 (Mean = 11.03, Median = 11). ISTH-BAT based bleeding score for 6 months after prophylaxis ranged from 5 to 17 (mean = 9.94, Median = 10). ISTH-BAT based score before and after 6 months of prophylaxis was compared using paired student t test separately in each group of patients. No improvement of ISTH-BAT based bleeding score was found in Group A patients (p value = 0.67) which was statistically insignificant. However improvement of ISTH-BAT based score was found in Group B patients (p value = 0.006) which was statistically significant (Fig. 4).

A strong positive correlation was found between ABR and ISTH-BAT based bleeding score before prophylaxis (rho = 0.86, p value = 0.000). Also a strong positive correlation was found between ABR and ISTH-BAT based bleeding score during prophylaxis (rho = 0.90, p value = 0.000).

Discussions

The patient population in our study comprised 19 severely hemophilic (57.57%) and 14 moderately hemophilic (42.42%) boys and there was no case of mild hemophilia. No significant difference was found between the annual joint bleeding rate of severe and moderate hemophilic group (p = 0.99). Also 30 (90.9%) children had developed target joint(s). Our results are probably because only children with significant limitation of physical activity and severe bleeding phenotypes sought prophylactic treatment because of factors like poor socioeconomic condition and poor transport facility from home to treatment center.

In our study Knee joint was found to be the most involved target joint (52.9%) followed by elbow joint (38.2%). There were only 2 cases of ankle joint (5.9%) and 1 case of shoulder joint (2.9%) involvement. Results obtained in a study by Vikas Payal et al. knee joint was the predominant joint affected by hemarthrosis in 67.85% cases which is similar to our study. However ankle joint was involved in 51.78% cases and elbow joint was involved in 35.71% cases. Hip joint and shoulder joint involvement was seen in 12.5% and 5.35% cases respectively [10]. This may be because our study population was comparatively small.

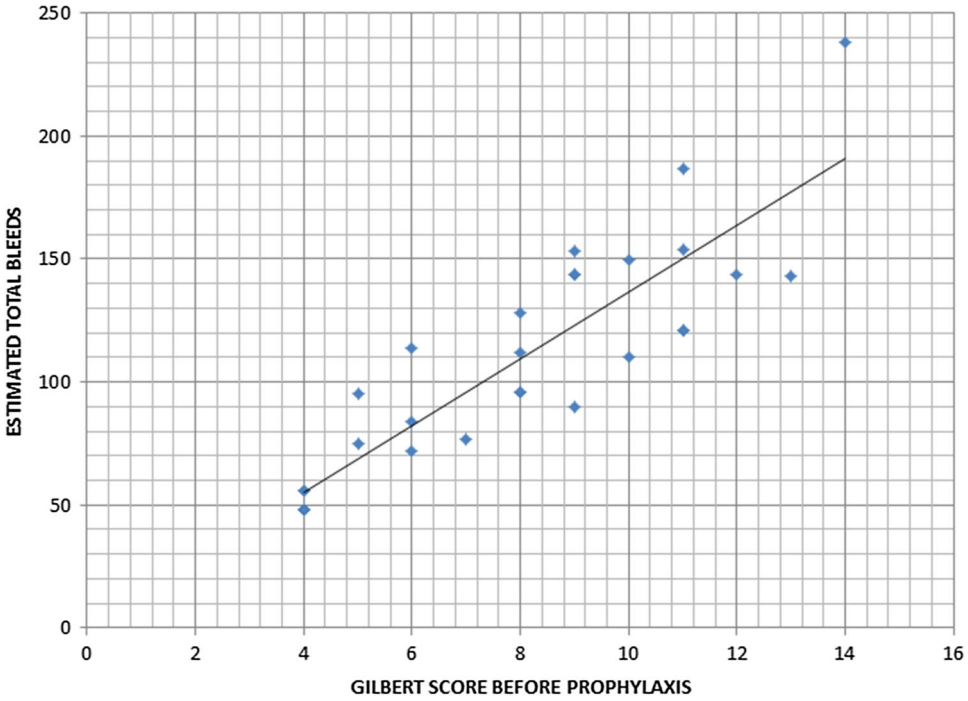

Fig. 2 Correlation of gilbert score with total estimated joint bleeds

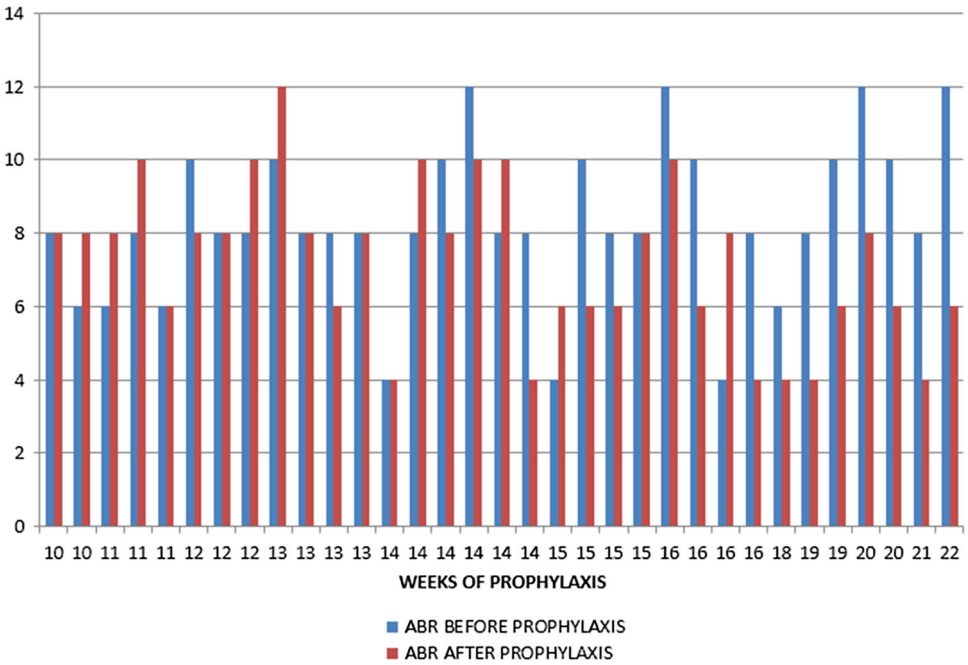

Fig. 3 Annualized bleeding rate before and after prophylaxis

Total number of weeks of prophylactic doses received by each child ranged from 10 to 22. (mean = 14.8, median = 14). None of the children could adhere to continuous prophylactic regimen of at least 45 weeks/year (in our study 23 weeks in 6 months) because of factors like low socioeconomic conditions and poor transport facility from home to treatment center. A positive correlation was found between age of the children with Gilbert Score (rho = 0.56) and between annual joint bleeding rate and Gilbert Score (rho = 0.52). No correlation was found between age of first onset of joint bleeding and Gilbert Score (rho = − 0.23 $p = 0.23$) and between percentage of endogenous Factor Activity and Gilbert Score (rho = 0.07). Similar results were found by Hayam M. et al. in a study on 30 hemophilic patients where a significant positive correlation was found between the Gilbert score and the age of the patients and an inverse correlation was found between Gilbert score and factor activity level ($r = -0.538$, $P = 0.002$) [11]. These

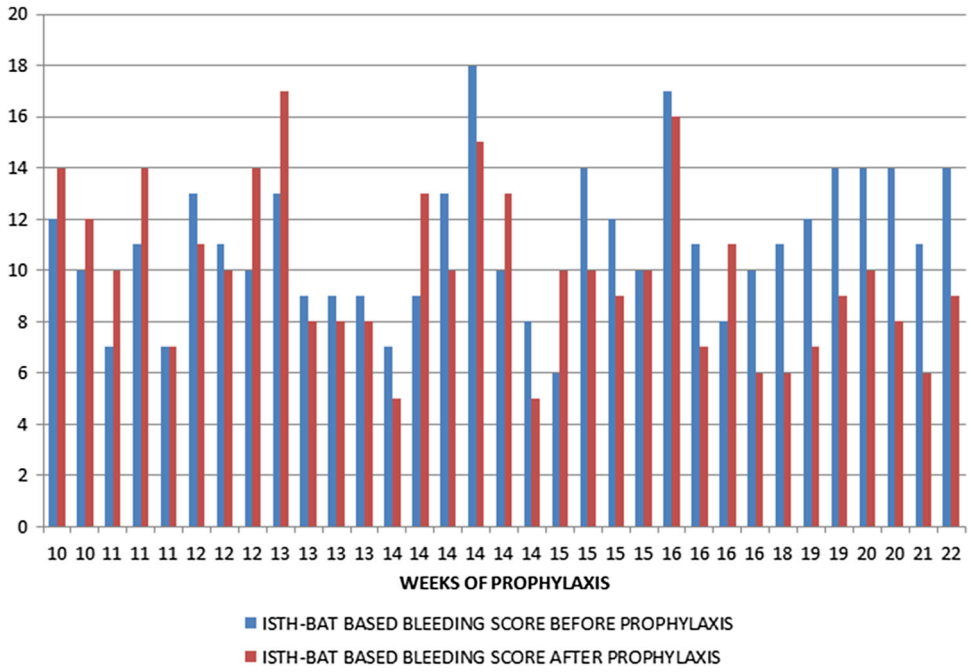

Fig. 4 ISTH-BAT based bleeding score before and after prophylaxis

results are probably because the severity of hemophilic arthropathy is multifactorial and also because among children of moderate hemophilia only those with severe joint bleeding phenotypes came to seek prophylactic treatment in our center. However a strong positive correlation was found between estimated total joint bleeds in the children and Gilbert Score (rho = 0.77) showing the progressive destructive nature of hemarthroses contributing to the severity of hemophilic arthropathy.

In our study Annualized Bleeding Score (ABR) before prophylaxis ranged from 4 to 12 (Mean = 8.3). ABR during prophylaxis ranged from 4 to 12 (Mean = 7.21). No improvement of ABR was found in Group A patients (p value = 0.87). However significant improvement of ABR was found in Group B patients (p value = 0.007). Similar results were found by Abraham et al. [12] in a study on 26 hemophilic patients where mean ABR reduced from 3 to 0 after 6 months of prophylaxis in twice weekly regimen. ISTH-BAT based bleeding score for 6 months before prophylaxis ranged from 6 to 18 (Mean = 11.03). ISTH-BAT based bleeding score for 6 months during prophylaxis ranged from 5 to 17 (mean = 9.94). No improvement of ISTH-BAT based bleeding score was found in Group A patients (p value = 0.67). However significant improvement of ISTH-BAT based score was found in Group B patients (p value = 0.006). These results indicate that a significant reduction in bleeding episodes can be achieved only if patients can sufficiently adhere to continuous prophylactic therapy regimen.

A strong positive correlation was found between ABR and ISTH-BAT based bleeding score before prophylaxis (rho = 0.86, p value = 0.000). Also a strong positive correlation was found between ABR and ISTH-BAT based bleeding score during prophylaxis (rho = 0.90, p value = 0.000). These results indicate that ISTH-BAT criteria can be used as a tool to score bleeding episodes in hemophilia.

Conclusion

Bleeding into joints is a hallmark of Hemophilia. In our study Knee joint was found to be the most involved target joint (52.9%) followed by elbow joint (38.2%). Arthropathies of both these joints lead to severe limitation of daily normal activities.

Development of chronic arthropathy is multifactorial. However a strong positive correlation was found between estimated total joint bleeds in the children and Gilbert Score (rho = 0.77). This indicates the cumulative irreversible pathophysiologic changes caused by repeated episodes of hemarthroses leading to development and worsening of chronic hemophilic arthropathy.

No significant improvement of ABR (p value = 0.87) and of ISTH-BAT based bleeding score (p value = 0.67) were found in patients who received prophylaxis for less than 15 weeks. However significant improvement of ABR (p value = 0.007) and of ISTH-BAT based bleeding score (p value = 0.006) were found in children who received prophylaxis for at least 15 weeks. These results indicate that a significant reduction in bleeding episodes can be

achieved only if patients can sufficiently adhere to continuous prophylactic therapy of twice weekly regimen.

A strong positive correlation was found between ABR and ISTH-BAT based bleeding score both before prophylaxis (rho = 0.86, p value = 0.000) and during prophylaxis (rho = 0.90, p value = 0.000). These results indicate that ISTH-BAT criteria can be used as a tool to score bleeding episodes in hemophilia.

A major limitation of our study was that none of the children could adhere to continuous prophylaxis protocol. Out of around 45 patients informed, 39 patients attended the hemophilia centre for prophylaxis of which 6 patients discontinued after 2 or 3 weeks and were excluded from the study. Factors like low socioeconomic conditions, cost of transport, poor transport facilities from place of residence to treatment center, absence from work for the parents for 2 days per week, repeated venous access were stated by the parents for discontinuation of therapy; poor accessibility being the most significant factor. Establishment of multiple hemophilia prophylaxis centres is being contemplated to overcome the problem of accessibility but lack of trained personnel poses a great obstacle to this policy. This calls for introduction of recent protocols like Home management in third world countries like India.

Compliance with Ethical Standards

Ethical Approval All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. The study was explained to all participants and their parents. Informed consent was taken from all the individual children as well as their parents included in the study.

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