Utilization evaluation of factor concentration and frequency of bleeds among patients with haemophilia “A” and haemophilia “B” in northwest Iran

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Original Article

Abstract

BACKGROUND: Hemophilia A and B are X-linked bleeding disorders which result in decreased blood levels of coagulants. According to some studies, Hemophilia Severity Score (HSS) is higher in severe Haemophilia A (HA) than in severe Hemophilia B (HB). The present study aimed to compare bleeding frequency and utilization of factor concentration in HA and HB patients.

METHODS: This was a single institution retrospective study, and we collected the data from records of our Hemophilia Clinic. The subjects consisted of 176 Hemophilia A and 35 Hemophilia B with moderate to severe conditions. All the patients used on-demand treatment with plasma derived factor concentrates. Chi-square, one sample T and Mann-Whitney U tests were used. All the calculations were performed with MedCalc Statistical Software version 12.1.4.

RESULTS: Overall admission rates for patients with Hemophilia A were 3.125/patient/year and for Hemophilia B were 0.77/patient/year ($P < 0.05$). The amount of factor concentration used by HA patients was 3731500IU of FVIII (21201.704 IU/patient/year), and 611000 IU of Factor IX, by patients with hemophilia B (17457.142 IU/patient/year). The difference in the usage of factor concentration was not statistically significant ($P = 0.57$).

CONCLUSIONS: The data suggested that these inherited coagulation disorders (Hemophilia A and Hemophilia B) have a different severity in clinical phenotype. Our findings correlate with findings by some other similar studies that have been published recently.

KEYWORDS: Hemophilia A, Hemophilia B, Factor Concentration, Utilization Evaluation

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Introduction

It has been traditionally known that the clinical manifestations of hemophilia A (HA) and hemophilia B (HB) are identical, and they cannot be differentiated without evaluating the specific factor VIII (FVIII) and factor IX (FIX) clotting activities.[1] The clinical diagnosis of hemophilia has been determined

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largely by the differences in bleeding type that is associated with the activity levels of coagulation factors VIII or IX. Recent studies have confirmed the validity of the original hemophilia classification by Biggs and MacFarlane in 1958[2,3] as well as the standard classification by the Scientific and Standardization Committee of the International Society on Thrombosis and Homeostasis in 2001.[4] However, it has been suggested that HA and HB may differ in terms of the severity of bleeding tendency.[5,6] More recently, a preliminary report found that tendency toward bleeding is more in patients with HA, so factor concentration consumption is more than HB with comparable plasma factor levels.[7] Moreover, using the validation frame of a composite score required assessment of the clinical severity of hemophilia. Schulman et al. found that HA is more severe than HB even at similar degrees of plasma factor deficiency.[8] Tagariello et al. revealed that patients with HA had a 3-fold higher risk of undergoing joint arthroplasty than patients with HB of the same severity.[5] However, since joint arthroplasty is an end-stage event and indicates severity of the disease, an evaluation of the frequency of bleeding would have been a better variable to compare HA with HB patients.[1]

Determining the number of bleeding is difficult, especially in patients on prophylaxis. These patients experience no or limited joint bleeding, and they tend to report every event/case of joint pain as bleeding. In contrast, patients receiving treatment on demand, especially those without home treatment, tend to arrive the hospital only with massive bleeding; they tend to ignore small joint bleeding. This effect should be recognized while defining the scores of phenotypes in clinical studies.[9] Since the severity and frequency of bleeding may be variable in hemophiliacs sharing the same factor activity so a mild bleeding should be considered as a possibility of severe hemophiliacs in 10-15% of cases.[10]

After adjusting for the difference in the in vivo recovery of factor concentrations, it has been shown that FIX has a much larger initial distribution volume than FVIII, leading to a lower in vivo recovery. This phenomenon can be explained by the rapid binding of FIX to the vascular endothelium. While assessing the dosage of FIX in hemophilia B, it should be considered that the in vivo recovery of FIX is approximately only 50% so the initial dosages required are higher than hemophilia A. Finally, the mean pharmacokinetic parameter values reported by several studies on adults show that the plasma half-life of FIX is longer than FVIII, so the interval between doses can be extended.[11] The primary outcome of our study was comparison between amount of FVIII and FIX consumption and admission rates in patients with HA and HB with any level of bleeding tendency.

Methods

This was a single institution retrospective study at Tabriz Haemophilia Treatment Center (HTC) in the Northwestern region of Iran. All published papers related to comparison of bleedings and clinical aspects of both HA and HB patients were considered. All eligible patients registered in our hemophilia treatment center were enrolled and their data were collected from October 2010 to September 2011. Our study was approved by the Ethical Committee of Tabriz University of Medical Sciences, Tabriz, Iran.

Confirmatory tests including one stage FVIII and FIX assays were performed by STA. In FVIII and FIX deficiency, immune-depleted plasma examination was implemented by STA analyzers suitable with these reagents (Diagnostica Stago, France). The presence of FVIII and FIX inhibitors were tested by Bethesda assay.

We examined the frequency of bleeding and factor consumption among patients with various levels of FVIII and FIX deficiency. A retrospective electronic medical record review of all patients treated in a single

Hemophilia Treatment Center was conducted. Adult patients (age ≥ 11 years), who had no history of high titer inhibitors and who were treated on demand exclusively since diagnosis, were considered to be eligible. Data were collected from the home infusion log records by patients and treatment records from our Hemophilia Treatment Center.

All the patients in this study were treated based on demand with plasma-derived factor concentrations. Data of 176 hemophilia A and 35 hemophilia B cases were categorized as severe (FVIII, IX < 1 IU dl^{-1}), moderate (FVIII, IX 1-5 IU dl^{-1}), and mild (FVIII, IX ≥ 5 IU dl^{-1}). HA patients were aged 11-74 years (32.29 ± 11.32 years), and HB patients were aged 12-70 years (28.77 ± 10.69 years).

Thus, bleeding was classified as joint bleeding or elsewhere than joint (muscular, soft tissue, and mucous membrane bleeding). The main criterion for factor treatment was the factor level required, which was 30%-60% (IU/dl) in both HA and HB for common bleedings, including hemarthrosis and hematoma. The results were compared with the Chi-square, one sample T and Mann-Whitney U tests. All calculations were performed with MedCalc Statistical Software version 12.1.4.0. Finally, the results of our study were compared with those of corresponding data from the literature. The results showed as Mean ± SEM and A P-value of 0.05 which was considered statistically significant. Normal distribution analysis was done by Kolmogorov-Smirnov test.

Results

Among 176 HA patients, mean FVIII levels were 0.14-15.50 IU/dl (4.18 ± 0.31). Mean FIX levels were 0.17-8.36 IU/dl (2.24 ± 2.23) in 27 HB patients. FVIII inhibitor mean levels were 0-1.60 BU (0.40 ± 0.08) and FIX inhibitor mean levels were 0-0.65 BU (0.10 ± 0.002) in 27 HB patients. Overall, 2.84% of HA and 7.40% of HB patients had low inhibitor titers. Among 176 HA patients in this study, the overall admission rate was 550 bleeding over 12 months comparing to 27 bleeding in 35 HB patients (in this study, admission rate and bleed rate have been used synonymously). There was a statistically significant difference between the HA and HB patients, with 3.125 bleeding/(patient·-year) for HA and 0.77 bleeding/(patient year) for HB patients (P = 0.031). The amount of factor concentrations (FVIII) used by HA patients was 3731500 IU (21201.704 IU/[patient year]), and 611000 IU of FIX by HB patients (17457.142 IU/[patient year]). The difference in the use of factor concentrations was not statistically significant (P = 0.570). Patients' characteristics are shown in tables 1 and 2.

Table 1. Comparison of age and factor concentrates used differences in two types of hemophilia

Type	Number	Age (year)	Bleed		Factor concentrates used	
			Per year	P	IU/Year	P
Severe HA	62	31.50 ± 8.79	320	0.040	3026000	0.110
Severe HB	16	25.18 ± 8.00	13		481500	
Moderate HA	57	31.21 ± 10.97	182	0.028	516500	0.090
Moderate HB	13	28.69 ± 7.75	-	0.009	67000	-
Mild HA	57	34.03 ± 13.74	48	0.760	189000	< 0.001
Mild HB	6	41.20 ± 10.69	-	0.005	62500	-

HA: Haemophilia A; HB: Haemophilia B; IU: International units

Table 2. Comparison of quantitative parameters between hemophilia A and B

Type	Number	Age (year)	Bleed			Factor concentrates used (IU)		
			Per	Patient/Year	P	Per	Patient/Year	P
HA	176	39.29 ± 11.32	550	3.125	0.031	3731500	21201.704	0.570
HB	35	28.77 ± 10.69	27	0.770	-	611000	17457.142	-

HA: Haemophilia A; HB: Haemophilia B; IU: International units

Discussion

Due to high cost and limited availability of factor concentrations in the Hemophilia Treatment Center, all patients in this study received treatment on demand with factor concentrates; therefore, determining the number of bleeding is probably more realistic in our study.

Even though severe HA and HB are classically considered to be identical from a clinical standpoint, the results of one study by Tagariello et al. provided evidence that the risk of undergoing joint arthroplasty is different for these two inherited coagulation disorders. The risk of patients with HA requiring arthroplasty was 3-fold higher, with no difference for the sites of the prosthesis.[5]

Whether there are different rates of bleeding and admission rates exist between the two types of hemophilia, there may be several possible reasons for these differences. One is that HB is caused by gene mutation that is less severe than the one causing HA, as demonstrated in the Italian database of mutations,[12] with only a relatively small proportion of null mutations (e.g. large deletions, nonsense mutations, or rearrangements).[5]

Although the sample size in this study was small and it represented 176 HA and 27 HB patients, our findings correlated with recently published findings by other groups. Similar to our findings, a study from central Scotland reported that the overall admission rates for patients with HA were 2-3 times higher than that for patients with HB at all levels of severity, with little difference in the rates between the levels of severity.[13]

The difference in factor concentrate usage was not statistically significant, both in our study as well as in analogous reports, as both groups used similar amounts of factor concentrate, which is related to the lower in vivo recovery of infused FIX compared to FVIII. The volume distribution of factor IX is twice than total plasma volume; hence, the recovery following the infusion is approximately 1% per unit per kilogram body weight while the recovery with the infusion of recombinant factor IX is 20% lower than that of the plasma derived concentration.[8,14] According to Nagel et al., primary prophylaxis may not be necessary for all patients with severe or moderate HB.[7] However, Klamroth et al. evaluated the regimen of replacement therapy within a 5-year period and revealed that 4/12 (33%) patients with HB had a history of intracerebral bleeding in comparison to 5/111 (5%) patients with severe HA. Their data suggested a milder bleeding type in patients with severe HB comparing to patients with severe HA; however, patients with severe HB may be at a higher risk for intracranial bleeding.[15] We believe that the importance of prophylaxis for patients with severe or moderate HB should be further studied because the risk of life-threatening bleedings is still high in both the coagulation disorders.

Nagel et al. collected data based on frequency of bleeding and factor concentration utilization over three years. According to their results, bleeding in HA patients is more frequently than HB patients, (14.4 vs. 8.63 bleeding/ [patient year]), although they used similar amounts of factor concentration per year, where the difference in factor concentrate usage was not statistically significant.[7] The study by Tagariello et al. also found that this difference was not due to confounding factors such as age and HIV or hepatitis C infection.[5]

This retrospective study has several limitations such as the lack of detailed patient histories, including molecular genotyping of HA and HB, evaluation of possible modulators such as FV G20210A and Prothrombin G20210 A. Failure to obtain all these data from patients, and other potential limitations, implicit in any retrospective survey.

Conclusion

In conclusion, our study showed that there was a statistically significant difference

between bleeding/(patient year), so in HA patients tendency toward bleeding is more than HB patients. Our findings may have potential clinical implications; in effect, they add corroborative evidence to the previous observations, which suggest that HB patients bleed less than HA patients.

Furthermore, it is not known if the lack of FVIII, comparing to FIX, results in more bleeding. Moreover, it is unclear whether the treatment for bleeding is less effective or the bleedings are more severe. Therefore, we suggest that clinicians should plan less primary prophylaxis for HB patients.

Due to the low prevalence of hemophilia, however data collection in a single-institution study is valuable, further studies with a larger sample size within multiple centers is strongly recommended.

Conflict of Interests

Authors have no conflict of interest.

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