ORIGINAL ARTICLE

Haemophilia care and outcome in a major haemophilia treatment centre in Malaysia

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ABSTRACT

Introduction/Objective: The management of potential treatment-related complications and bleeding events in haemophilia is challenging in developing countries. Providing optimal care among these patients improve their quality of life (QOL) and life expectancy. This study explores the demographic characteristics and treatment outcome in a major haemophilia treatment centre in Malaysia.

Materials and Methods: A total of 260 patients were recruited in this retrospective cross-sectional analysis. Clinical data, including treatment regimens and outcome, were collected and analysed.

Results: A total of 211 patients were diagnosed with haemophilia A (HA) (severe disease, 72.5%) and 49 patients had haemophilia B (HB) (severe disease, 65.3%). The median age was 31 (IQR;2-84) years. Majority of the patients had at least one episode of musculoskeletal bleeding since diagnosis. The mean annual bleeding event (ABE) was 4.91 (SD±6.07) in 2018. Target joints were identified in 80.4% of the patients. Chronic arthropathy and synovitis collectively accounted for more than half of the musculoskeletal complications. 30.1% of the patients had contracted hepatitis C with less than half received treatment. Thirty-one patients (16.8%) with severe haemophilia developed inhibitor and 12 patients successfully underwent immune tolerance induction. More than three-quarters of the severe haemophilia patients were treated with factor concentrate prophylaxis. The mean prophylaxis dose for HA and HB were 41.3 (SD±19.1) and 48.6 (SD±21.5) IU/kg/week, respectively. In patients with severe disease, prophylaxis significantly reduced the ABE (5.45,9.03;p=0.005).

Conclusion: The importance of utilising a low to moderate dose regimen as prophylaxis in haemophilic patients is highlighted in our study. Future studies should include QOL assessment will further improve the management in haemophilia.

KEYWORDS:
Haemophilia, Malaysia, bleeding disorder, prophylaxis

INTRODUCTION

Haemophilia is a group of X-linked recessive disorders, affecting the coagulation factors responsible for the clotting mechanism. The two most common forms of haemophilia are haemophilia A (HA) and haemophilia B (HB). The management of potential treatment-related complications and bleeding events in haemophilia is challenging in developing countries. Providing optimal care among these patients improve their quality of life (QOL) and life expectancy. With a total population of 31.5 million in Malaysia, the estimated total number of patients of all types of haemophilia was 1,075 in 2018, making the prevalence of 3.4 per 100,000 population.[1]

The use of recombinant factors and plasma-derived factors has significantly improved the overall clinical outcomes and survival among patients with haemophilia (PWH). However, exposure to the factor replacement may lead to the production of alloantibody (inhibitor) against the factor protein and the management for this group of patients is challenging, requiring the use of expensive bypassing agents such as factor VIII inhibitor bypassing agent (FEIBA) and activated factor VII. The incidence of transfusion-transmitted infection, such as hepatitis B, hepatitis C, and human immunodeficiency virus (HIV), is now significantly reduced but is not negligible. Complications involving the musculoskeletal system which are observed frequently in haemophilia include acute intraarticular haemorrhage, intramuscular haemorrhage, recurrent intraarticular bleeding, chronic synovitis, and chronic arthropathy. All these complications will have a significant impact on their quality of life, besides creating an enormous economic burden on the national health care system.

Clinical data about haemophilia is scarce in Malaysia. This study aimed to determine the demographic characteristics, treatment characteristics, and its effectiveness in preventing complications among patients diagnosed with haemophilia in a major haemophilia treatment centre in Malaysia. To the best of our knowledge, this is the first published study on the epidemiological profile of haemophilia in Malaysia. The outcome of this study will serve to improve the overall future management of haemophilia.

MATERIALS AND METHODS

Study design and population

This is a retrospective cross-sectional study conducted in a Malaysian tertiary hospital, Hospital Ampang, Ministry of Health Malaysia, Selangor treating PWH. All patients

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diagnosed with HA and HB treated and followed up from January till December 2018, were recruited. Patients from the central region in Peninsular Malaysia were followed up in our haemophilia treatment centre (HTC). Patients with other congenital clotting deficiency, acquired haemophilia, and of uncertain diagnosis were excluded. Socio-demographic data, clinical characteristics, complications, treatment regimens, and outcomes were collected from the medical records using a standardised data collection forms. This study was registered with the National Medical Research Register, Malaysia, and the ethical approval for this study was obtained from the Medical Research and Ethical Committee (MREC), Ministry of Health Malaysia (NMRR-19-2979-51363).

A patient with haemophilia was defined as any patient who was diagnosed with HA or HB in the presence of bleeding tendency and confirmed by laboratory evidence of low coagulation factor activity level. Patient with HA was any patient with factor VIII deficiency since birth and patient with HB was any patient with factor IX deficiency since birth. The severity of haemophilia was divided into mild, moderate, and severe based on the activity level and this applies for both HA and HB.

Mild haemophilia is defined as factor activity between 5 to 40% of normal factor activity; moderate haemophilia include factor activity between 1 to 5% of normal factor activity, and severe haemophilia is defined as factor activity less than 1% in the bloodstream. Target joint is defined as the joint with recurrent bleeding, as diagnosed by the physician and recorded in the medical record. This includes joint with at least 3 or more bleeding events occurring within 3 to 6 months period. Annual bleeding event is defined as the total bleeding events documented for each patient for one year.

Statistical Analysis

The statistical software Statistical package for Social Science (SPSS) version 22 (SPSS Inc., Chicago, IL, USA) was used to analyse all the data collected and extracted. Categorical data were expressed as frequencies and percentages and continuous data was expressed as mean ± standard deviation. Independent student's t-tests were used to compare group means of continuous dependent variables while the Kolmogorov-Smirnov Test of Normality was used to test the distribution of a sample. All p values are 2-sided and p values <0.05 were considered statistically significant.

RESULTS

Socio-demographic data and clinical features

260 patients were recruited with a median age of 31 (range, 2-84) years old. The median age of diagnosis was 2 (range 1 – 73) and 6 years old (range 1 – 39) for HA and HB, respectively. Majority of the site of the first bleed was unknown due to missing documentation. All patients were males, and 52.7% were Malays followed by Chinese (34.6%), and Indians (10%). A total of 211 patients were diagnosed with HA with 72.5% of them had severe disease, while 49 patients had HB (severe disease, 65.3%). About two-third had a significant family history. Details of clinical characteristics are illustrated in Table I.

The overall mean annual bleeding event in 2018 was 4.91 (SD6.07). Chronic arthropathy and synovitis collectively accounted for more than half of the musculoskeletal complications with only 39% of them undergoing intervention such as radioisotope synovectomy and arthroplasty. Target joints were identified in 81.5% of patients with HA and 83.7% of patients with HB. Other complications included intracranial bleeding (15.6%), surgical bleeding (8.1%), and gastrointestinal bleeding (7.6%) in HA. Conversely, surgical bleeding (16.3%) was the second commonest complication in HB followed by intracranial bleeding (10.2%), and gastrointestinal bleeding (8.2%) (Table II).

Seventy-eight patients with HA and HB contracted hepatitis C. Among these patients, three had co-infection with hepatitis B and two had co-infection with human immunodeficiency virus (table II). Only 32 patients were treated for their underlying hepatitis C, while treatment was exempted for eight patients due to spontaneous seroconversion. Patients contracted with hepatitis B and HIV were all treated accordingly with appropriate antiviral therapy.

Thirty-one patients with HA and two patients with HB developed inhibitors. Among these, 16 patients with HA underwent immune tolerance induction (ITI) with 12 of them (75%) successfully achieved ITI and resumed on regular prophylaxis. Fifteen patients with inhibitor were treated with on-demand/prophylaxis bypassing agents. Treatment with clotting factor concentrate (CFC) is illustrated in Table III. Prophylaxis with factor concentrate was started on 80.4% of the patients with severe HA and 78.1% of the patients with severe HB, respectively. Plasma-derived factor concentrate remained the main treatment option in our centre. The mean prophylaxis dose calculated for HA was 41.3 (±19.1) IU/kg/week and HB was 48.6 (±21.5) IU/kg/week in 2018. In patients with severe haemophilia A and B, prophylaxis significantly reduced the annual bleeding event (5.45, 9.03; p=0.005). Five patients were treated with emicizumab and two patients were recruited in fitusiran clinical trial.

DISCUSSION

Haemophilia results in lifelong bleeding disorder with factor replacement being the key to achieving a better quality of life in these patients. With the advent of factor prophylaxis in moderate to severe haemophilia, this has significantly reduced the incidence of bleeding, especially joint haemorrhage, and hence, improved the joint function and enabled PWH to lead a healthy and active lifestyle. Haemophilia Joint Health Score (HJHS) is a validated tool in assessing joint function with higher score indicates poorer joint health.[2] A study from Singapore reported a median score of 5.5 and 4 in their cohort of younger children (<10 years old) and older children (11-20 years old), who were mostly on prophylactic therapy and these findings were consistent with most developed countries.[3] Unfortunately, HJHS assessment is not routinely carried out in our centre, and thus a comparison cannot be made. Nonetheless, reduction in bleeding events among patients using prophylaxis may indirectly translate into better joint health as majority of our patients had at least one episode of

Table I: Socio-demographic data and clinical characteristic of patients with haemophilia

	Mild n (%)	Moderate n (%)	Severe n (%)	Missing n (%)	Total, N (%)
Haemophilia A					
Severity	28 (13.3)	28 (13.3)	153 (72.5)	2 (0.9)	211 (100)
Age distribution					
0-10	1	1	4	0	6 (2.8)
11-20	4	4	30	1	39 (18.5)
21-30	9	8	39	1	57 (27)
31-40	3	3	45	0	51 (24.2)
41-50	3	8	22	0	33 (15.6)
Above 50	8	4	13	0	25 (11.8)
Ethnicity					
Malay	10	12	85	1	108 (51.2)
Chinese	12	12	54	1	79 (37.4)
Indian	6	2	10	0	18 (8.5)
Others	0	2	2	0	4 (1.9)
Inhibitors					
Yes	0	1	29	1	31 (14.7)
No	28	26	124	1	179 (84.8)
Missing	0	1	0	0	1 (0.5)
Haemophilia B					
Severity	7 (14.3)	10 (20.4)	32 (65.3)	0	49 (100)
Age distribution					
0-10	0	0	2	0	2 (4)
11-20	1	1	6	0	8 (16.3)
21-30	1	5	5	0	11 (22.4)
31-40	2	2	10	0	14 (28.6)
41-50	2	1	9	0	12 (24.5)
Above 50	1	1	0	0	2 (4)
Ethnicity					
Malay	4	6	19	0	29 (59.2)
Chinese	2	1	8	0	11 (22.4)
Indian	1	3	4	0	8 (16.3)
Others	0	0	1	0	1 (2)
Inhibitors					
Yes	0	0	2	0	2 (4.1)
No	5	10	30	0	45 (91.8)
Missing	2	0	0	0	2 (4.1)

Table II: Bleeding events and treatment complications among patients with haemophilia

Types of bleeding	Haemophilia A N = 211 n (%)	Haemophilia B N = 49 n (%)
Musculoskeletal (At least one episode)	187 (88.6)	41 (83.7)
Presence of target joints	172 (81.5)	35 (71.4)
Number of target joints		
1	50	14
2	63	8
3	32	8
>3	24	5
Psoas bleeding	36 (17.1)	5 (10.2)
Intracranial bleeding	33 (15.6)	5 (10.2)
Surgical bleeding	17 (8.1)	8 (16.3)
Gastrointestinal bleeding	16 (7.6)	4 (8.2)
Annual bleeding event (mean±SD)	4.91 (±6.07)	
Treatment complications		
Hepatitis C	66 (31.3)	12 (24.5)
Hepatitis B	3 (1.4)	1 (2)
HIV	2 (0.9)	0 (0)

SD: Standard deviation; HIV: human immunodeficiency virus

Table III: Treatment characteristics for patients with haemophilia

Characteristics	Mild n=28 (%)	Moderate n=28 (%)	Severe n=153 (%)
Haemophilia A			
• On-demand CFC	27 (96.4)	18 (64.3)	29 (19.6)
• Prophylaxis CFC	1 (3.6)	10 (35.7)	123 (80.4)
Treatment for target joints			
Radiofrequency ablation	0	2	31
Arthroplasty	0	2	5
Dysarticulation	0	0	1
Others	0	0	5
Missing	0	0	1
	Mild n=7 (%)	**Moderate n=10 (%)**	**Severe n=32 (%)**
Haemophilia B			
• On-demand CFC	7 (100.0)	6 (60.0)	7 (21.9)
• Prophylaxis CFC	0 (0)	4 (40.0)	25 (78.1)
Treatment of target joints			
Radiofrequency ablation	0	1	5
Arthroplasty	0	0	2
Dysarticulation	0	0	0
Others	0	0	1
Missing	0	0	0
Mean CFC in prophylaxis		**Dose (iu/kg/week)**	
• PwH A		41.3 (± 19.1)	
• PwH B		48.6 (± 21.5)	

CFC: clotting factor concentrate; PwH: patients with haemophilia

musculoskeletal bleeding and more than 70% of them had target joints. This will require validation from future studies.

British Society of Haematology (BSH) and World Federation of Haemophilia (WFH) have recently updated their guidelines in the management of haemophilia, with recommendations including the approach, timing, and dosing for patients requiring prophylaxis.[4,5] All severe and moderate haemophilia patients with factor level of <3% should be considered for prophylaxis.[4] Low, intermediate, and high dose prophylaxis were explored to achieve "zero" bleeding. The used of plasma-derived and recombinant factors has been the mainstay of factor replacement for many years, and in Malaysia, providing coagulation factor concentrates (CFC) as prophylaxis remains a huge financial burden with limited access to novel agents. As our public health system consists of tax and government-run primary health care centres and hospitals with support mainly through general revenue and taxation collected by the federal government,[6] the economic burden remains a challenge in managing these patients. This is in addition to the common challenges faced including catheter-related infections, development of factor inhibitors, and viral infections from plasma-derived replacement factors.

A variety of regimens are used by different countries for the initiation of prophylaxis therapy of which there is long term data.[7] The Canadian protocol,[8,9] Malmo (high dose) protocol[10] or Utrecht (intermediate dose) protocol[10] had been practised widely in prophylaxis therapy. With financial limitation, utilisation of a low dose prophylaxis regimen is common to meet the demands of severe haemophilia patients.[11-13] The approach in our centre is by initiating patients on 10-15IU/kg of body weight two to three times per week in low dose regimen and escalate them according to the breakthrough bleeds. This has shown good results with a significant reduction in the annual bleeding events in those with the severe phenotype in which prophylaxis significantly reduced the ABE from 9.03 to 5.45 (p=0.005) compared to those who were on-demand factor replacement. This benefit was observed despite a low to moderate dose replacement schedule with a mean CFC dose 41.3 (±19.1) IU/kg/week in HA and 48.6 (±21.5) IU/kg/week in HB. A similar trend of reduction in bleeding rates was observed in the other studies utilising the low dose approach.[11-13] However, a direct comparison to our study is not feasible due to the different protocols in the delivery of factor replacement and assessment of bleeding. Unfortunately, although the vast majority of our patients with severe disease were treated with regular prophylaxis, one-fifth of them still opted for on-demand replacement due to various reasons, including logistics and reluctance by our patients. Patient education and compliance is important to further reduce the bleeding events in our haemophilia population.

The acquisition of inhibitors is common among those on plasma-derived factors with the highest risk in the first 20 exposure days. Among severe HA, the cumulative incidence of all inhibitors was 26.8% with the plasma-derived factors and 44.5% with the recombinant factors. Out of this, 18.6% and 28.4% had high titres (>5 Bethesda units) respectively.[14] In HB, inhibitor development is less frequent (1.5-3%) but associated with significant morbidity especially an increased bleeding risk.[15] The current management strategies in patients with inhibitors include the provision of a bypassing agent, non-factor replacement (e.g. emicizumab, fitusiran, and concizumab) commonly through enrolment into clinical trials, and ITI. To date, ITI is the only proven method of which eradication of inhibitors are possible.[16] Various ITI protocols with high dose infusions of factors had resulted in 60-90% success rates in HA[17,18] and 30% in HB.[19] In our cohort of patients, 31 HA and 2 HB patients developed inhibitors, a 12.7% cumulative incidence which is comparable to another study.[20] Herein 16 patients (HA) were subjected to ITI with

75% of them were successful in eliminating the inhibitor. Therefore, ITI is generally feasible and should be practised in this group of patients.

Another complication surrounding plasma-derived factor replacement is the presence of blood product-related infections. Improvements seen in haemophilia treatment over time will see these patients having a longer life span, and thus, have an increased risk of infections with repeated exposure of plasma-derived factors.[21] The availability of commercial plasma-derived factor, which is highly purified and undergone strict processing method, significantly reduces the risk of contracting transfusion-transmitted infections and has almost eradicated it. Despite that, it remains a risk not to be neglected. WFH in their recent annual global survey reported HIV and hepatitis C infection continues to be a challenge even in developed countries, such as Japan and France based on the prevalence of infective cases reported with regards to PWH.[22] In our cohort of patients, a proportion of patients who contracted hepatitis C, received cryoprecipitate and fresh frozen plasma during the early 1990s when screening was not widely available. Only half of the patients received treatment for hepatitis C and this might be related to the course of treatment, which was previously prolonged and patient needs to be committed before treatment initiation. With the availability of oral antiviral agents, the proportion of patients receiving treatment likely will increase significantly. The rates of other viral infections were fortunately low.

STUDY LIMITATIONS AND CONCLUSION

This study is limited by its retrospective nature and unavailability of quality of life assessment of the patients. Despite being the major HTC covering almost one-quarter of the haemophilia population in Malaysia, a comprehensive study for the whole of Malaysia would be beneficial.

Nonetheless, our study has provided an insight into the demographics of the haemophilia population and highlighted the importance of prophylaxis in patients with moderate to severe haemophilia albeit the use of low to moderate dose regimen. We should anticipate increasing age-related health issues as more older patients, e.g., those with cardiovascular morbidity and renal impairment)among them. Understanding our current haemophilia landscape will eventually improve future care of haemophilia patients.

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