Original Article

Incidence of Subclinical Joint Bleeding among Hemophilia A Patients with Prophylaxis Therapy in Babylon Hereditary Blood Disease Center

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Abstract

Background: Hemophilia A is a sex-linked blood disease characterized by recurrent joint bleeding, which may progress eventually to disability in adolescence in the absence of prophylaxis therapy. Even, many patients may develop joint damage which suggests subclinical or hidden joint hemorrhage, which can be detected by ultrasound (U/S) scan and magnetic resonance imaging. **Objectives:** It showed the incidence of subclinical joint bleeding in hemophilia A with prophylaxis therapy and its correction with blood parameters such as hemoglobin, packed cell volume, mean corpuscular hemoglobin concentration, mean corpuscular volume. **Materials and Methods:** It is observational, cross-sectional study on 30 hemophilia patients, aged 3–18 years with mean age ranging 10.27 ± 3.552 years who were on prophylaxis therapy with no clinical feature of arthropathy. These hemophilia patients were evaluated clinically by using U/S scan and magnetic resonance imaging (MRI). The study period was from January 2023 to July 2023. All studied patients were evaluated for anemia clinically and confirmed by Hb and PCV and other red blood cell indices including MCV, MCHC, and serum ferritin. All patients underwent joint U/S scan and magnetic resonance imaging. **Results:** It showed that 26.7% and 46.7% of patients had subclinical bleeding diagnosed by U/S scan and MRI, respectively, whereas there was no significant statistically difference among all blood parameters including PCV, MCV, and MCHC despite mild reduction of serum ferritin. **Conclusion:** It showed that 26.7% of hemophiliac patients developed subclinical bleeding diagnosed by U/S scan and 46.7% by MRI.

Keywords: Arthropathy, hemophilia A, magnetic resonance imaging, prophylaxis, subclinical bleeding, U/S scan

Introduction

Hemophilia A (HA) is a sex-linked disease resulting from a deficiency in the clotting factor VIII (FVIII). Severe form of HA may lead to recurrent joint bleeding that eventually may progress to disability in adolescence in the absence of prophylaxis.[1]

The most commonly affected body parts are elbows, knees, and ankles joints, and its repetitive bleeding may lead to hemophilic arthropathy which can present as soft tissue swelling, damage of cartilage, and subchondral bone erosion with loss of range of motion, and may accompany with chronic pain, leading to disability.[2]

The efficacy of prophylaxis therapy in the treatment of severe form of hemophilia A children has been universally acknowledged.[3] There are three forms of prophylaxis therapy, depending primarily on the time at which patients receive therapy.[3,4]

Primary prophylaxis

Treatment is begging after the onset of the first joint bleeding, before the appearance of documented joint disease, and before 3 years of age.

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Secondary prophylaxis

Therapy can be started after the onset of at least two joint bleeding or after the age of 3 years without joint disease documented by physical examination and plain radiograph.

Tertiary prophylaxis

Treatment can be began after the beginning of documented joint disease.

However, primary and secondary prophylaxis are the most effective in joint safety, while tertiary prophylaxis has benefits. All three approaches are now shown in the most recent guidelines for the hemophilia treatment.[3]

Prophylaxis is universally accepted as the therapy of choice for patients with hemophilia. Early prophylaxis is found to be higher than on demand therapy in decreasing the risk of overall bleeding and improving joint health and quality of life.[4]

Primary prophylaxis is the current gold standard in hemophilia care for avoiding bleeding and protection from joint damage. Dosage and treatment regimens vary across countries and owing to the limited introduction of factor concentrates and financial resources in developing countries; therefore, many children, adolescent and young adult with hemophilia are managed with secondary or tertiary prophylaxis.

According to this proof, there are many patients presented with joint degenerative changes despite prophylaxis therapy, suggesting that subclinical hemorrhage or hidden joint may occur even with this type of management due to repetitive bleeding episodes, manifested as joint discomfort; therefore, early diagnosis of joint bleeding whether subclinical or clinical preferably during childhood is important to help in prevention joint damage and disability.[5,6]

The current outcome measures are unable to find out subclinical bleeding and may give the false impression of the absence of early joint changes.[7]

Table 1: Characteristic of study patients

Factors	Number	%
Age		
<10 years	12	40%
≥10 years	18	60%
Sex		
Males	30	100%
Females	0.0	0.0%
Prophylactic therapy		
Primary	10	33.4%
Secondary	20	66.6%
Dose of prophylaxis		
Primary	20–30 unit/kg/twice/weeks (25 unit/kg)	
Secondary	30–40 unit/kg/2–3/weeks (35 unit/kg)	

Magnetic resonance imaging (MRI) is the best standard imaging study, but its use in daily clinical practice is restricted due to its increased cost, unavailability in many centers, and the sedation is needed in hemophilia children even some abnormalities are better diagnosed with an MRI for subchondral cysts, cartilage loss, and hemosiderin precipitate.[5]

Compared with MRI, ultrasound (U/S) has been able to diagnose and evaluate the most relevant marker of disease activity such as joint effusion, synovial hypertrophy and osteochondral changes. The benefits of U/S scan include shorter time examination, lesser cost, easy availability, no sedation in children, and the possibility of examining many joints in the same session.[5]

Aim of study

The aim of this study was to show the incidence of subclinical joint bleeding among hemophilia A with prophylaxis detected by U/S scan and MRI, together with its correlation with blood parameter such as Hb, serum ferritin, platelets count, MCV, and MCHC.

Materials and Methods

It is an observational, cross-sectional study on 30 patients with severe hemophilia A, aged 3–18 years with a mean age ranging 10.27 ± 3.552 years, who were on prophylaxis therapy, with no clinical feature of arthropathy. The patients had no history of recent joint bleeds in last 8 months before study done, with dosing schedules: FVIII 20-40 IU/kg, that administer two or three time a week..

Prophylaxis was given according to the physical activity, the presence of bleeding, availability of drug, and treatment adherence.

The history of joint bleeding was gathered from the patients' diary and confirmed by medical records.

All patients attended the Babylon hereditary blood disease center for a routine follow-up visit during the study period from January 2023 to July 2023

Inclusion criteria

1. Hemophilia A severe type (factor level of less than 1%).
2. On primary and secondary prophylaxis.
3. Age: 3–18 years.

Table 2: Blood parameter of study patients

Blood parameter	Mean ± SD
Hb (gm/dL)	10.25 ± 3.552
Platelets count × 10^3	273.35 ± 108.311
Serum ferritin (ng/dL)	10.837 ± 7.537
MCV (fL)	76.927 ± 4.721
MCHC (g/dL)	32.213 ± 9.478

Exclusion criteria

1. They had inhibitor or history of inhibitor of both type (low of 1–5 Bethesda unit (BU) or high of more than 5 BU).
2. Tertiary prophylaxis.

All studied patients were evaluated for anemia clinically and confirmed by Hb and PCV, and other red blood cell indices included MCV, MCHC, and serum ferritin and they were sent for joint U/S scan and MRI Table 1.

Clinical history

Epidemiological data and clinical history were gotten from Babylon Hemophilia medical record, including age, age of diagnosis, target joint, number of joint bleedings, and dose of factor VIII.

Target joint is defined as a joint with two or more spontaneous bleeding points which have occurred within a period of six consecutive months.[2]

All joints were evaluated and should be within normal examination, no pain, no swelling or hotness, and no erythema.

4 mL of blood aspirated and separated into 2cc of blood in EDTA tube for Hb, PCV%, MCV, MCHC and the other 2cc were sent in plain tube for serum ferritin estimation.

Complete blood count was done using hematology analyzer Mindray-BC 5300 within 30 min of collection samples.[8]

Serum ferritin was evaluated by using (VIDAS device) ferritin device which is automated test for ferritin determination using enzyme linked fluorescent assay technique by ferritin kit.[9]

Normal level of serum ferritin is between 7 and 150 ng/mL.

Hb (hemoglobin level: normal level 11–15 g/dL).

MCV: mean corpuscular volume (normal value 81–96 fL) can be directly measured by automated hematology analyzer, collected through EDTA tube.

MCHC: mean corpuscular Hb concentrate (normal value 31.8–35.4 g/dL) Table 2.

All patients sent to U/S and MRI scanning of target joints. U/S was performed by a radiologist specialist to look for joint hematoma or bleeding (minimal/mild–moderate/severe), joint damage by looking at cartilage (normal/cartilage damage) and bone (normal/irregularity of subchondral bone). Those patients with joint damage characterized by bone cyst, bone irregularity were excluded from study.

Hemophiliac arthropathy staging[10]

Stage 0: normal joint, stage 1: hematoma (swelling of soft tissue and erythema), stage 2: osteoporotic changes and early subchondral cyst, stage 3: large subchondral cyst, stage 4: cartilage loss with narrowing of the joint (stages 0 and 1 were included in the study only).

Table 3: Frequency of sub clinical bleeding cases among study patients

Factors	Number	%
U/S	30	
Normal	22	73.3
Abnormal	8	26.7
MRI	30	
Normal	16	53.3
Abnormal	14	46.7
Prophylactic	10	
Primary	2	20
Abnormal U/S	4	40
Abnormal MRI		
Secondary	20	
Abnormal U/S	6	30
Abnormal MRI	10	50
Age		
Abnormal U/S		
<10 years (12 pts)	3	25
≥10 years (18 pts)	5	27.7
Total (30 pts)	8	
Abnormal MRI		
<10 years; 12 pts	5	41.6
≥10 years (18 pts)	9	50
Total (30 pts)	14	
Abnormal MRI		54.54
Normal U/S (22 pts)	12	
Abnormal U/S (8 pts)	8	100

U/S = ultrasound

Table 4: Mean blood parameter among cases with normal and abnormal U/S and MRI

Blood parameter	U/S			MRI		
	Normal	Abnormal	*P*-value	Normal	Abnormal	*P*-value
Hb	11.882 ± 1.036	11.213 ± 0.066	0.1	11.80 ± 0.98	11.60 ± 1.01	0.6
Platelets	273.895 ± 121.956	283.100 ± 62.536	0.84	260.60 ± 109.40	292.100 ± 109.62	0.43
S. ferritin	11.282 ± 7.69	9.611 ± 7.287	0.5	9.95 ± 5.89	8.71 ± 6.95	0.3
MCV	76.62 ± 4.60	77.75 ± 5.24	0.5	76.23 ± 4.67	77.62 ± 4.83	0.4
MCHC	32.74 ± 10.93	30.75 ± 30.20	0.6	34.40 ± 12.87	30.02 ± 3.15	0.21

MRI was done after given sedation to patients older than 10 years and general anesthesia for younger 10 years of age. It persisted for 20–30 min, and it was performed by a technician and specialist consultant radiologist.

Statistical analysis

Data were analyzed by statistical package of social sciences (SPSS version 24.0, Chicago, Illinois, United States). Discrete variables, presented as number and percentage, were analyzed using chi square test. *P* value <0.05 is considered significant.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients' parents' verbal and analytical approval before sample was taken. The study protocol, the subject information, and consent form were reviewed and approved by a local ethics committee according to the document number 6 on January 1, 2023.

Results

60% of patients are aged above 10 years, 66.6% were on primary prophylaxis, and the doses of primary was 20–30 unit/kg and secondary was 30–40 unit/kg.

The patients was diagnosed as subclinical bleeding by U/S and MRI in 26.7% and 46.7% respectively, they classified into primary prophylaxis in 10 patients and secondary one in

20 patients. The most of cases got bleeding was diagnosed through MRI in 4/10 (40%) in primary and 10/20 (50%) in secondary form, their ages with subclinical bleeding mostly older 10 years. All cases with abnormal U/S had abnormal MRI Table 3.

There was no significant statistically difference between those with and without subclinical bleeding detected by both U/S and MRI despite mild reduction of serum ferritin and MCHC.

Discussion

Primary prophylaxis is the standard treatment in hemophilia patients. Early diagnosis of joint damage is very important whether symptomatic or asymptomatic to prevent deterioration of the joint and subsequent disability. Repeated hemorrhage of the joint produces synovial hypertrophy and progressive osteochondral changes that may result in degenerative arthropathy.[5,11,12]

In the current study, they showed 60% of patients older than 10 years, 33.4% had primary prophylaxis and 66.6% secondary prophylaxis, and 100% were men as hemophiliac A is X linked disease.

The primary prophylaxis initiated earlier with onset of diagnosis in severe form, whereas those patients were having irregular therapy and lived far away from center, poor family, and poor income and sometimes because of unavailability of drugs may result in developing frank bleeding of more than two times making the patients on secondary prophylaxis which may lead later to joint disability.

There was a shortage in hemophiliac drugs; therefore, they used low dose prophylaxis between 20 and 30 unit/kg twice weekly in primary prophylaxis and increased dose in secondary prophylaxis to 30–40 unit/kg twice weekly or occasionally three times a week depending on a clinical and imaging study of joint bleeding and kept the patients on close follow-up.

Our results were slightly similar to that done in Argentina[6] which showed that 44.3% and 55.7% primary and secondary prophylaxis, respectively. This can be explained by the prophylaxis therapy in both centers based on patients life style and physical activity[13] and availability of factor VIII.

There were 8/30 (26.7%) of patients developed joint subclinical bleeding diagnosed by U/S scan, in comparison to 14/30 (46.7%) detected by MRI.

Ultrasound scan is not so sensitive for the identification of early stage of bleeding especially in first 24 h of its onset; even it may show negative especially if little bleeding and also it gives us less detail of intraarticular bleeding[14,15] making the current results regarding U/S was lower; therefore, repeated U/S or alternatively an MRI should be considered better.[15] MRI is highly sensitive to look for early stage of bleeding, sign of disease activity, and effective to perform a comprehensive evaluation of the joint surfaces.[11,15,16]

MRI may require sedation in hemophilia children, costly with long waiting lists, cannot be used for serial follow-up studies compared to U/S which is important as excellent diagnostic tool to diagnose joint bleeding, even can assess synovial hypertrophy and osteochondral changes in joints that are almost totally asymptomatic.[11] This give us that MRI is not routinely used.

This U/S results is compatible to study done in Argentine 22.1%[17] and lower than Indonesian studies which found that 50.85%[2] in 2015 and 47.5% in 2017[18] as Indonesian patients used on demand therapy with no prophylaxis.[18]

Higher results diagnosed by MRI 46.6% explained, the MRI has enable to detect early joint bleeding (even in first 24 h) and the details of its joint images including effusion,[15] even can identify whether bleeds have occurred in a joint because of hemosiderin precipitation.[16]

The results of the current study regarding MRI is similar to study done in some areas of Canada,[19] because of not full prophylaxis dose given due to shortage of treatment and it is higher than in Netherlands 16%,[7] in Canadian 26%[19] due to introduction of full prophylaxis therapy in these centers.[7]

The risk of bleeding occurred more in secondary prophylaxis 30% (6/20) by U/S and 50% (10/20) in MRI, compared to primary prophylaxis showing 2/10 (20%) and 4/10 (40%), respectively. This is similar to study results done in Argentine (72.9%) patients developed joint bleeding in secondary prophylaxis and 21.3% in primary prophylaxis[6] and in many area of world as.[20-22]

This can explain that the secondary prophylaxis may commence after two or more joints bleeding and prior onset of proven joint damage; therefore, it is likely that this bleeding has caused subclinical, and therefore the aims are to limit the consequence of this damage through prevention further bleeding and maximizing its function.[23]

The positive cases occurred mostly older than 10 years of age in both U/S and MRI studies as secondary form of prophylaxis had hidden bleeding manifested mostly in older children (early initiation of prophylaxis together with periodic monitoring of joint status, physical activity, regularity to treatment, and earlier inhibitors diagnosed can prevent this complication).[24]

There was abnormal MRI (including soft tissue swelling, erythema in 12/22 patient (54.54%) of normal U/S and 8/8 patient 100% of abnormal U/S which indicated that MRI is highly sensitive to reveal the sign of disease activity,[11] reverse to U/S which is negative or less sensitive in the first day of hemorrhage especially if it is small.[15,16]

There was no significantly statistically different of all blood parameters to normal and abnormal joint status detected by U/S or MRI. The current result was compatible to a study done in Iraq, Babylon showing 75% of patients developed iron deficiency without anemia Table 4.[25]

This indicated that mild or subclinical bleeding might have occurred and may be associated with iron deposition in the joints due its release from Hb which initially binds to ferritin whereas unbound iron will have direct toxic effects on tissue modulate inflammatory and immune function.[25]

The current study is one of the important limitations which is relatively smaller in size.

Conclusion

1. Hemophilia patients got subclinical joint bleeding diagnosed by U/S in 26.7% and MRI in 46.7%.
2. There was no significant statistically difference between those with and without subclinical bleeding detected by both U/S and MRI despite mild reduction of serum ferritin and MCHC.

Recommendation

Early diagnosis of subclinical bleeding is very important in children, in order to avoid later long-term functional impairment; therefore, periodic monitoring of the joint status in hemophilia patients has been recommended through use of U/S and MRI imaging studies.

Conflict of interest

There are no conflict of interest.

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