THE STUDY OF INFLUENCE OF PLATELET DYSFUNCTION ON CLINICAL PHENOTYPE OF HEMOPHILIA

By

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ABSTRACT

Background: Hemophilia is an X-linked heritable coagulopathy with an overall prevalence of approximately 1 in 10,000 individuals. Hemophilias are rare X linked hereditary bleeding disorders. Platelets may be among the determinants of variability in bleeding phenotype.

Objective: To evaluate the platelet function tests in patients with hemophilia, and to explore the influence of platelet dysfunction on hemophilia bleeding score.

Patients and Methods: The study was conducted on 40 hemophilic patients and 20 normal persons as a control in outpatient clinics at Kafr El-Sheikh Governorate Hospitals and Al-Azhar University Hospitals (Al-Hussein and Sayed Galal) to evaluate the platelet function tests in patients with hemophilia, and to explore the influence of platelet dysfunction on hemophilia bleeding score.

Results: The majority of cases (35 patients 87.5%) were type A and (5 patients 12.5%) were type B. As regard to hemophilia scoring system (HSS), 3 patients (7.5%) were type 1, 19 patients (47.5%) were type 2 and 18 patients (45%) were type 3. Bleeding from the knee occurred in the majority of patients (77.5%), from the elbow occurred in 32.5%, from the ankle occurred in 5%, from the vagina occurred in 15% and from the nose and the gum occurred in 7.5%. Platelets and maual platelet count showed insignificant difference between both groups. Platelets aggregation tests (ADP) test, collagen and restocetin agonists test) were significantly lower in cases group than control group. Prothrombin time (PT), international normalized ratio (INR), bleeding time (BT) showed insignificant differences between both group. On the other hands, activated partial thromboplastin time (APTT) significantly prolonged cases group than control group. No hemophilia C cases were detected in our study.

Conclusion: There was a statistical significant relationship between bleeding phenotype in hemophilia B and platelet function. Diagnosis of hemophilia was confirmed by factor VIII assay for hemophilia A and factor IX assay for hemophilia B.

Keywords: Hemophilia, Platelet Dysfunction, Clinical Phenotype.

INTRODUCTION

Although many patients with hemophilia may have exactly the same residual clotting factor level, the clinical disease phenotype may vary greatly. This variation may be related to different genetic mutations responsible for hemophilia, environmental influences and co-inheritance of polymorphisms affecting the coagulation system in hemophilia *(Traivaree et al., 2011).*

While thrombin generation is severely impaired in persons with hemophilia, primary hemostasis, i.e. platelet function, has been generally considered to be normal. However, some studies reported prolonged bleeding times in hemophilia, suggesting that also primary hemostasis is affected *(Faircloth et al., 2017).*

An influence of platelet function on clinical phenotype was suggested, which might contribute in part to variations in bleeding tendency in hemophilic patients with similar factor levels. However, the available evidence is currently limited and no clear correlations between platelet function parameters and clinical phenotypes have been demonstrated. The impact of alterations of platelet function in hemophilia remains to be better defined. Another interesting role of platelets in hemophilia has been reported recently by establishing a novel gene-therapeutic strategy using platelets as a delivery system for FVIII, showing promising results in animal models. This review gives an overview on the currently published literature on platelet function and the potential roles of platelets in hemophilia *(Lyde et al., 2015).*

The primary goal of this study was to evaluate the platelet function tests in patients with hemophilia and to explore the influence of platelet dysfunction on hemophilia bleeding score.

PATIENTS AND METHODS

The study was conducted on 40 hemophilic patients and 20 normal persons as a control in outpatient clinics at Kafr El-Sheikh Governorate Hospitals and Al-Azhar university Hospitals (AL-Hussein and Sayed Galal) to evaluate the

platelet function tests in patients with hemophilia and to explore the influence of platelet dysfunction on hemophilia bleeding score. The population of the study included patients suffering from Hemophilia A and B aged (12-50) years old.

Inclusion criteria:

• Known patients with Hemophilia A and B.

• Age between 12 – 50 years.

• Patients not receiving anti platelet drugs.

Exclusion criteria:

• Patients complaining from Hemophilia aged less than 12 years and more than 50 years.

• Patients with splenomegaly.

• Patients with chronic liver diseases.

• Patients with chronic renal diseases.

• Patients with cardiac diseases that receiving antiplatelet drugs.

Ethics and Patient Consent: All the procedure followed Al Azhar University ethics committee regulations. An informed written consent was taken from every patient before collecting any information or starting any procedure.

Hemophilia scoring system:

1. Age at first joint bleed or arthropathy.

2. Treatment requirement (i.e. annual clotting factor use).

3. Annual bleeding frequency.

Group	A	B	C
Score	3	2	1

Investigations done:

1. Complete Blood Count.

2. Manual platelet count.

3. Platelet aggregation tests by using platelet aggregometry with ADP, Collagen and Ristocetin agonists.

4. Prothrombin time (PT), international normalization ratio (INR).

5. Bleeding time (BT).

6. Activated partial thromboplastin time (aPTT).

7. Measurement of FVIII activity in homphilia type A cases.

8. Measurement of FIX activity in homphilia type B cases.

Statistical analysis:

Statistical analysis was done by SPSS v25 (IBM Inc., Chicago, IL, USA). Normality of data was checked with Shapiro-Wilks test and hsitograms. Numerical variables with normal distribution were presented as mean, standard deviation (SD), range and compared between the two groups utilizing Student's t- test. . Numerical variables with abnormal distribution were presented as median, range and compared between the two groups utilizing Mann-Whitney (U) test. Categorical variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate. P value < 0.05 was considered significant.

RESULTS

The study was conducted on 40 hemophilic patients and 20 normal persons as a control in outpatient clinics at Kafr El-Sheikh Governorate Hospitals (Al Obour Hospital and Kafr El-Sheikh General Hospital) and Al-Azhar university Hospitals (Al-Hussein and Sayed Galal).

Patients' characteristics (age, sex and weight) showed insignificant difference in both groups (P = 0.683, 0.552 and 0.082 respectively) **(Table 1)**.

Table (1): Patients' characteristics in both groups

Parameters	Groups	Cases (n = 40)	Control (n = 20)	P value
Age (years)	Mean ± SD	22.45 ± 11.7	23.6 ± 6.11	>0.05 #
	Range	12-44	14-30	
Sex	Male	31 (77.5%)	16 (80%)	>0.05
	Female	9 (22.5%)	4 (20%)	
Weight (kg)	Mean ± SD	56.93 ± 21.48	67.1 ± 20.05	>0.05 #
	Range	29-100	35-95	

compared by Mann-Whitney test

As regard to type of hemophilia, 35 patients (87.5%) were type A and 5 patients (12.5%) were type B. As regard to HSS, 3 patients (7.5%) were type 1, 19 patients (47.5%) were type 2 and 18 patients (45%) were type 3. As regard to site of bleeding, bleeding from the knee occurred in 31 patients (77.5%), from the elbow occurred in 13 patients (32.5%), from the ankle occurred in 2 patients (5%), from the vagina occurred in 6 patients (15%) and from the nose and the gum occurred in 3 patients (7.5%) **(Table 2)**.

Table (2): Type of hemophilia, HSS and site of bleeding in the cases group

		Cases (n = 40)
Type of hemophilia	**A**	35 (87.5%)
	B	5 (12.5%)
Hemophilia scoring system	**Type 1**	3 (7.5%)
	Type 2	19 (47.5%)
	Type 3	18 (45.0%)
Site of bleeding	**Knee**	31 (77.5%)
	Elbow	13 (32.5%)
	Ankle	2 (5%)
	Vaginal	6 (15%)
	Nose	3 (7.5%)
	Gum	3 (7.5%)

HSS: Hemophilia scoring system

TLC, platelets and maual platelet count showed insignificant difference between both groups (P value = 0.541, 0.057 and 0.481). Hemoglobin was significantly lower in the cases group than the control group (P < 0.001) **(Table 3)**.

Table (3): Complete blood count (CBC) in both groups

Parameters \ Groups		Cases (n = 40)	Control (n = 20)	P value
Hemoglobin (g/dL)	**Mean ± SD**	10.12 ± 1.63	13.8 ± 1.32	**<0.001**
	Range	7.2-13	12-16	
TLC (*10³/mm³)	**Mean ± SD**	9.03 ± 2.02	9.38 ± 2.15	>0.05
	Range	6-13.3	4.3-12	
Platelets (*10³/mm³)	**Mean ± SD**	196.03 ± 73.17	238 ± 89.54	>0.05 [#]
	Range	100-329	180-410	
Manual platelets count (*10³/mm³)	**Mean ± SD**	229.83 ± 78.51	243.6 ± 52.22	>0.05 [#]
	Range	130-411	180-326	

TLC: Total leucocytic count # compared by Mann-Whitney test

Platelets aggregation tests (ADP, collagen and restocetin agonists) were significantly lower in cases group than control group (P = 0.016, 0.011 and 0.049 respectively) **(Table 4)**.

Table (4): Platelets aggregation tests in both groups

Parameters	Groups	Cases (n = 40)	Control (n = 20)	P value
ADP test	**Mean ± SD**	52.65 ± 21.9	68 ± 23.87	**0.016* #**
	Range	10-84	22-85	
Collagen test	**Mean ± SD**	61.98 ± 18.07	75.4 ± 25.38	**0.011* #**
	Range	29-94	30-103	
Restocetin agonists test	**Mean ± SD**	60.6 ± 26.12	75.6 ± 26.4	**0.049* #**
	Range	8-90	30-110	

ADP: Adensoine DiPhosphate # compared by Mann-Whitney test

PT, INR, BT showed insignificant differences between both groups except APTT that showed significant increase in cases group than control group (P < 0.001) **(Table 5)**.

Table (5): Bleeding profile in both groups

Parameters	Groups	Cases (n = 40)	Control (n = 20)	P value
Prothrombin time	**Mean ± SD**	14.89 ± 1.21	14.4 ± 0.6	>0.05
	Range	13-17	13.5-15	
International normalization ratio	**Mean ± SD**	1.11 ± 0.1	1.08 ± 0.1	>0.05
	Range	0.9-1.3	0.9-1.2	
Activated partial thromboplastin	**Mean ± SD**	65	35	**<0.001**
	Range	24-80	34-58	
Bleeding time	**Mean ± SD**	1.21 ± 0.3	1.2 ± 0.41	>0.05 #
	Range	1-2	1-2	

PT: prothrombin time, APTT: activated partial thromboplastin, INR: international normalization ratio, BT: bleeding time, # compared by Mann-Whitney test

Factor VIII activity was done in 35 cases of homphilia type A with mean±SD 25.06 ± 31.86, median 10 and range between 5 and 95%. Factor IX activity was done in 5 cases of homphilia type B with mean ± SD: 5.6 ± 0.55, and range between 5 and 6% **(Table 6)**.

Table (6): Activity of factor VIII and factor IX in cases groups

Factor VIII (n = 35)	**Mean ± SD**	25.06 ± 31.86
	Median	10
	Range	5-95
Factor IX (n = 5)	**Mean ± SD**	5.6 ± 0.55
	Range	5-6

DISCUSSION

In our study, patients' characteristics (age, sex and weight) were comparable in both groups. As regard to type of hemophilia, the majority of cases 87.5% were type A and 12.5% were type B. This was supported by many studies found that hemophilia A is more common than hemophilia B. In most of the studies, hemophilia A constituted around 80% of

total hemophilias *(Ling et al., 2010, Uddin et al., 2010* and *Karim et al., 2013). Mansouritorghabeh (2015)* stated that hemophilia A or classical hemophilia accounts for about 80% of all hemophiliacs. Similarly, out of the total hemophilia patients, included in a study by *Mishra et al. (2016)*, type A and B hemophilia patients were 88.3% and 11.7%, respectively. The percentage of hemophilia type A patients was higher than type B in both the age groups.

In our study, as regard to HSS, 7.5% were type 1, 47.5% were type 2 and 45% were type 3.

Many scores were used to assess the severity of hemophilia symptoms. In study by *Qasim et al. (2013)*, 43.13% patients had severe degree of disease, 37.2% patients were diagnosed to have moderate degree of disease and 19.6% had mild disease.

Borhany et al. (2011) documented that majority of hemophiliacs had moderate severity (52.0%) both in homphilia type A (HA) and homphilia type B (HB). *Tonbary et al. (2010)* showed that severe manifestations were reported in 76.7%, followed by moderate severity in 17.2%.2.

In our study, bleeding from the knee occurred in the majority of patients (77.5%). From the elbow occurred in 32.5%, from the ankle occurred in 5%, from the vagina occurred in 15% and from the nose and the gum occurred in 7.5%.

In agreement with the present study, *Sharma et al. (2016)*, 38.8% had no complaints related to the disease. 61.11% presented with manifestations such as bleeding from soft tissues or joints, swelling or pain the joints etc. Knee is

most common site of repetitive bleeding and hemarthrosis followed by ankle (27.27%). 12.03% had involvement of more than one joints, while 6.06% presented with bleeding from gums.

In harmony with current study, *Qasim et al. (2013)* reported that, clinical features included prolonged bleeding after injury in 98% of patients, and 90% had hematomas at different body sites. Hemarthrosis (bleeding in the joints) was noted in 86% of the patients. Rest of the patients had prolonged bleeding after tooth extraction, epistaxis, bleeding from gums, deep bleeding, malena and hematuria. Knee joint was the most commonly involved joint (47.83% episodes).

In our study, platelets and maual platelet count showed insignificant difference between both groups. This correlated with a study done by *Sadaria et al. (2016)* who showed that platelet count of all patients was ranging from 1,50,000 to 491,000 /cmm which was within normal range.

In our study, hemoglobin was significantly lower in the cases group than the control group, which correlated well with study done by *Sinha et al. (2012)* showing hemoglobin was significantly lower in 25% of cases. This decrease in hemoglobin could be explained by loss of blood due to repeated bleeding episodes. *Ahmed et al. (2015)* stated that patients with hemophilia are more prone for iron deficiency and presents with iron deficiency anaemia.

Moreover, *Poongavanam et al. (2017)* showed that iron deficiency is common in patients with hemophilia, and it is related with increased severity of the disease due

to repeated episodes of spontaneous bleeding.

In disaccordance with our study, a retrospective study by *Hoffman and Monroe (2010)* found haemoglobin count of patients with hemophilia A and B ranged from 6g% to 14.2 g%. Another different result was reported by *Parthiban et al. (2015)* showed that, the hemoglobin level of patients with hemophilia A ranged from 7.8 g % to 14.6 g % and for hemophilia B ranged from 9.6 g % to 12.8 g%.

In our study, platelets aggregation tests (ADP test, collagen and restocetin agonists test) were significantly lower in cases group than control group. These findings were indicative of a concomitant platelet function defect in severe hemophilia. As baseline and post-stimulation expression of a-granular P-selection and d-granular CD 63 were similar in hemophiliacs and controls. Acquired storage pool deficiency is regarded an unlikely cause for the reduced platelet reactivity. Platelet–collagen interaction is mediated via the glyco-protein (GP) receptor Ia/IIa (a2b1 integrin), and the immunoglobulin superfamily receptor GP VI. The role of further potential collagen receptors remains to be determined. GP Ia/IIa and GP VI are constitutively expressed on the platelet surface in relatively low numbers, with a well-recognized up to 10-fold variation of the GP Ia/IIa expression occurring normally. GP Ia/ IIa has a major role in platelet adhesion and anchoring. GP VI is principally responsible for signaling and platelet activation. The activation of GP VI facilitates the binding of collagen to GP Ia-IIa.39,40

Deficiencies of GP Ia/IIa and GP VI are associated with decreased platelet adhesion and manifest as a mild bleeding disorder *(Maziri et al., 2016)* Similarly, *Tarandovskiy et al. (2013)* demonstrated through thromboelastography that platelet activity was involved in hemophilia phenotype and significantly changed.

In disagreement with current study, *van Bladel et al. (2011)* stated that the percentages of activated platelets after maximal ADP stimulation in all patients with hemophilia were comparable to those in healthy controls. They found that platelet responsiveness to ADP stimulation of patients with severe hemophilia and mild-moderate hemophilia did not differ from that of healthy controls for patients with severe and mild-moderate hemophilia, respectively.

In our study, Prothrombin time (PT), International normalization ratio (INR), and bleeding time (BT) showed insignificant differences between both groups. On the other hands, Activated partial thromboplastin time (APTT) significantly prolonged cases group than control group. This supported the view that the clotting time is not recommended as a reliable indicator of abnormal haemostasis and may be normal even in severe hemophilia as suggested by various authors

This correlated well with study done by *Sadaria et al. (2016)* which stated that PT is normal in all patients with hemophilia as extrinsic pathway is intact in hemophilia.

APTT was prolonged in all cases of hemophilia A and B with an average of 88 sec, similar to the mean APTT value of 80 seconds as reported by *Jennings et al.*

(2013). Also, the prolonged APTT values correlated with *Uddin et al. (2010).* The prolonged APTT with normal PT and bleeding time are typical findings in study by *Lippi et al. (2012)* which in line with our study.

In accordance with our study, a retrospective study by *Hoffman and Monroe (2010)* found that Prothrombin time was normal in all of these patients. *Taki and Shirahata (2012)* found that APTT prolonged in all the patients with hemophilia as it involves disruption of the intrinsic pathway of coagulation.

In accordance with our study, retrospective study by *Sadaria et al. (2016)* found Factor VIII level reduced (<50%) in all patient of hemophilia A. Normal range for factor VIII was 50% to 150%. Factor IX level reduced (<50%) in all patient of hemophilia B.

CONCLUSION

Diagnosis of hemophilia is confirmed by factor VIII assay for hemophilia A and factor IX assay for hemophilia B.

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دراسة تأثير إعتلال الصفائح الدموية على النمط الظاهري السريري للهيموفيليا

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خلفيـــة البحـــث: الهيموفيليـا اعـتلال تخثـر وراثـي مـرتبط بالكروموسـوم X، وانتشـاره العـام حـوالي 1 مـن كـل 10000 فـرد. وقـد تكـون الصـفائح الدمويـة مـن بـين محـددات التباين في النمط الظاهري للنزيف.

الهـدف مـن البحـث: تقيـيم إختبـارات وظـائف الصـفائح الدمويـة لـدى مرضـى الهيموفيليا وإستكشاف تأثير ضعف الصفائح الدموية على درجة نزيف الهيموفيليا.

المرضـى وطـرق البحـث: أجريـت الدراسـة علـى 40 مريضـاً بالهيموفيليـا و 20 شخصـاً طبيعيـاً كعنصـر حـاكم فـي العيـادات الخارجيـة بمستشـفيات محافظـة كفـر الشـيخ ومستشـفيات جامعـة الأزهـر (الحسـين وسـيد جـلال) لتقيـيم إختبـارات وظـائف الصـفائح الدمويـة لـدى مرضـى الهيموفيليـا ولاستكشـاف تـأثير ضـعف الصـفائح الدموية على درجة نزيف الهيموفيليا.

و قـد خضـعت جميـع الحـالات للحصـول علـي التـاريخ الكامـل والفحـص السـريري، ونظـام تسـجيل الهيموفيليـا، وتعـداد الـدم الكامـل، واختبـارات تـراكم الصـفائح الدمويـة باسـتخدام قيـاس تـراكم الصـفائح الدمويـة مـع اختبـارات تـراكم الصـفائح الدمويـة، ومنبهـات الكـولاجين والريستوسـيتين، ووقـت البروثـرومبين، والثرومبوبلاسـتين الجزئـي المنشـط ونسـبة السـيولة المعدلـة، ووقـت النـزف، وقيـاس نشـاط العامـل الثـامن فـي حـالات الهيموفيليـا مـن النـوع أ والعامـل التاسـع فـي حـالات الهيموفيليا من النوع ب.

نتـائج البحـث: كانـت غالبيـة الحـالات (35 مريضًـا 87.5٪) مـن النـوع أ و 5 مرضى (12.5٪) مـن النـوع ب. فيمـا يتعلـق بـنظام تسـجيل الهيموفيليـا، وكـان 3 مرضـى

(7.5 %) مــن النــوع 1، وكـــان 19 مريضًـــا (47.5 %) مــن النــوع 2 و 18 مريضًـــا (45 %) مــن النــوع 3. حــدث نزيــف مــن الركبــة فــي الجسـد فــي31 مريضــاً (77.5%)، ومــن الكــوع فــي 13 مريضــاً (32.5%)، ومــن الكاحــل فــي مريضيــن (5%)، ومــن المهبــل حــدث فــي 6 مرضــى (15%) ومــن الأنــف واللثــة عنــد 3 مرضــى (7.5%). كمــا أظهــر عــدد الصــفائح الدمويــة فرقــا مهمــا إحصــائيا بــين المجمــوعتين. وكانــت إختبــارات تــراكم الصــفائح الدمويــة وإختبــار منبهــات الكــولاجين والريستوســيتين) أقــل بشــكل ملحــوظ فــي مجموعــة الحــالات مقارنــة بالمجموعــة الحاكمــة. وأظهــر كــل مــن وقــت البروثــرومبين، ونســبة الســيولة المعدلــة، ووقــت النــزف إختلافــات غيــر مهمــة إحصــائيا بــين كلتــا المجمــوعتين. مــن ناحيــة أخــرى، كــان الثرومبوبلاســتين الجزئــي المنشــط أطــول بشــكل ملحــوظ فــي مجموعــة الحــالات عــن المجموعــة الضــابطة. ولــم يتم الكشف عن حالات هيموفيليا ج في دراستنا.

الاســتنتاج: ظهــرت علاقــة ذات دلالــة إحصــائية بــين الــنمط الظــاهري للنزيــف فــي هيموفيليــا "ب" ووظيفــة الصــفائح الدمويــة. ووجــود خلــل فــي وظيفــة الصــفائح الدمويــة يتضــمن تنشــيط الكــولاجين الــذي يحــدث فــي مرضــى الهيموفيليا. ويــتم تأكيــد تشــخيص الهيموفيليــا عــن طريــق قيــاس العامــل الثــامن للهيموفيليــا "أ" والعامــل التاســع للهيموفيليا "ب."

الكلمات الدالة: الهيموفيليا، ضعف الصفائح الدموية، النمط الظاهري السريري.