Fibrinolysis in idiopathic menorrhagia

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ABSTRACT

Objective: the role of fibrinolysis in idiopathic dysfunctional uterine bleeding (IDUB).
Design: prospective clinico-haematological study.
Setting: patients were collected in Albatool maternity teaching hospital; a haematological study was conducted in Ibn Sina teaching hospital in Mosul from 10th January to 10th of June 2004.
Participants: 53 patients with mean age of 40.5 years and a range of 15-54 years, complaining of idiopathic dysfunctional uterine bleedings(IDUB) served as experimental group, and 30 presumed healthy women served as a control group, their ages were between 18-45years. After exclusion of organic causes, drugs, IUCD, medical causes, and bleeding tendency, blood samples were tested for haemoglobin, plasma D-dimer test and plasma fibrinogen.
Results: D-dimer test was positive in 16 out of 53 cases (30.2%) of experimental group (Group 1). It was significantly positive ($p< 0.005$) in cases of idiopathic menorrhagia compared to the control group. D-dimer test was significantly positive in those with prolonged duration of vaginal bleeding >7days, compared to those with heavy periods and short duration of vaginal bleeding ($p<0.05$), D-dimer test was negative in the remaining cases (group II). The fibrinogen level was significantly lower in patients with positive D-dimer ($p<0.05$). Antifibrinolytic agent tranexamic acid was given to all patients in both groups; 93% of women responded to the treatment in group 1, while the response in group II was 54%.
Conclusion: Idiopathic menorrhagias appear to be due to increased fibrinolytic activity; such patients are likely to benefit from antifibrinolytic agents.

Keywords: Menometrorrhagia, dysfunctional uterine bleeding, fibrinolysis.

الخلاصة

الأهداف: ملاحظة نسبة تحلل الليفين عند المريضات المصابات بالنزف الرحمي اللانمطي بسبب تحلل الليفين .
خطة العمل: دراسة سريرية مرضية (أمراض الدم المستقبلية) .
مكان وزمان البحث: نفذت الدراسة في مختبر أمراض الدم في مستشفى ابن سينا التعليمي في الموصل ولمدة ستة أشهر ابتداء من كانون الثاني ٢٠٠٤م .
المشاركون: مجموعة من المريضات اللواتي أصبن بنزف رحمي لا نمطي إلى العيادة الاستشارية لمستشفى البتول التعليمي مع مجموعة من النساء كمجموعة ضابطة .
القياسات المستخرجة: تم إجراء الاختبارات التالية ، اختبارات الدم الأساسية ، اختبار الـ د ـالمزدوج في بلازما الدم ومقدار مولد الليفين .
النتائج: نتائج تفاعل موجبة لفحص الـ د-المزدوج في بلازما الدم لدى ١٦ امرأة من مجموع ٥٣ أي بنسبة ٣٠%، وكان هذا التفاعل موجباً بأهمية إحصائية مقارنة مع المجموعة الضابطة . كذلك فهو ذو أهمية إحصائية بالنسبة للمريضات ذوات الدورة الشهرية الطويلة (أكثر من ٧ أيام) مقارنة مع المريضات ذوات الدورة الشهرية الأقصر (اقل من ٧ أيام) . مستوى مولد الليفين المنخفض كان ذا أهمية إحصائية في المرضى ذوي التفاعل الموجب لاختبار د-المزدوج مقارنة مع المجموعة الثانية الذين لديهم تفاعل سالب لاختبار د-المزدوج والمجموعة الضابطة . أعطى العقار المانع لتحلل الليفين إلى كل المريضات وتبين أن ٩٣% منهن تجاوبن في المجموعة الأولى مقارنة بنسبة ٥٤% في المجموعة الثانية .
الاستنتاجات: حالات النزف الرحمي اللانمطي ممكن أن يكون لديهن استجابة جيدة للأدوية التي تمنع تحلل الليفين وقد لوحظ تجاوب ملموس .

Menorrhagia is defined as blood loss of 80ml or more per period[1]. It is still one of the commonest symptoms that bring patients to the gynecological clinics[2]. One of the fascinating aspects of menstruation is that menstrual blood does not clot and the endometrium has a high fibrinolytic activity; the fibrinolytic activity is enhanced in women with idiopathic dysfunctional uterine bleeding[3,4]. Menorrhagia has been attributed to a number of different causes. The incidence of coagulation disorders has been found to be almost 20% in adolescents with IDUB[5]. The endometrium possesses an active fibrinolytic system, and fibrinolytic activity is greater in the endometrium of women with menorrhagia than it is in the endometrium of women with menstrual blood loss in the normal range[4]. The former patients had defect in the regulators of the fibrinolytic system, accurate diagnosis of such disorder is essential to the design of appropriate therapeutic regimen[6,7]. Haemostasis of the endometrium is directly related to the functions of platelets and fibrin. Deficiencies in either of these components result in menorrhagia. Thrombi are seen in the functional layers but are limited to the shedding surface of the tissue. Fibrinolysis limits the fibrin deposits in the unshed layer. Accurate diagnosis of such disorder is essential to the design of appropriate therapeutic regimen as suggested by taking fibrinolytic inhibitors (e.g. tranexamic acid)[8-12]. Antifibrinolytic agents provide a rational and effective treatment, reducing the degree of menstrual loss by about 50%[4,12,13]. The D-dimer test utilizes a monoclonal antibody that recognizes a cross -linked fibrin epitope. The D-dimer assay is often used to assess the presence of disseminated intravascular coagulation (DIC). Generation of D-dimer requires action of both thrombin and plasmin and thus is specific for clot formation followed by lysis. Thus, the D-dimer assay is more specific for DIC than the fibrinogen/fibrin degradation product assay[14,15].

SUBJECTS AND METHODS

Subjects: Fifty three women were selected with a mean age of 40.5 years and a range of 15-54 years from the out patient clinic with idiopathic menorrhagia (the studied group). Patients were evaluated by taking a comprehensive history, including details of quantity, rhythm and duration of bleeding, medical problems such as diabetes mellitus and hypertension were considered, the method of contraception, pregnancy complications and drug history.We select our cases after general and local examination for organic and endocrinal abnormalities, pelvic ultrasonography, luteal phase progesterone, thyroid function studies, and diagnostic curettage were done.

Control group: 30 presumed healthy women aged between 18-45 years, they were not taking any medications.

Methods: Plasma D-dimer test was done by using a commercially available kit (biomerieux/FDP slidex direct–73101/France). Rapid latex agglutination slide test for the qualitative determination of the D-dimer reaction was done. Plasma fibrinogen concentration was done by using commercially available kit (biomerieux/fibrinomat-68452/France) that depends on the clot-based method of Clauss[9,16]. Haemoglobin and platelet count were done according to Dacie and Lewis. Thrombocytopenic women were excluded from the study. The control group were tested for plasma fibrinogen and D-dimer. Statistical analysis was done by using the chi square test and the t-student test.

RESULTS

The mean haemoglobin level was 105g/L with a range of 69-135g/L. Anaemia was observed in 30/53 (56.6%) of cases. Most women were married; four women were single unmarried. Plasma fibrinogen, Hb levels and platelet counts of patients and controls are shown in (Table 1).

Table (1): *Plasma fibrinogen, haemoglobin levels and platelet count in different groups.*

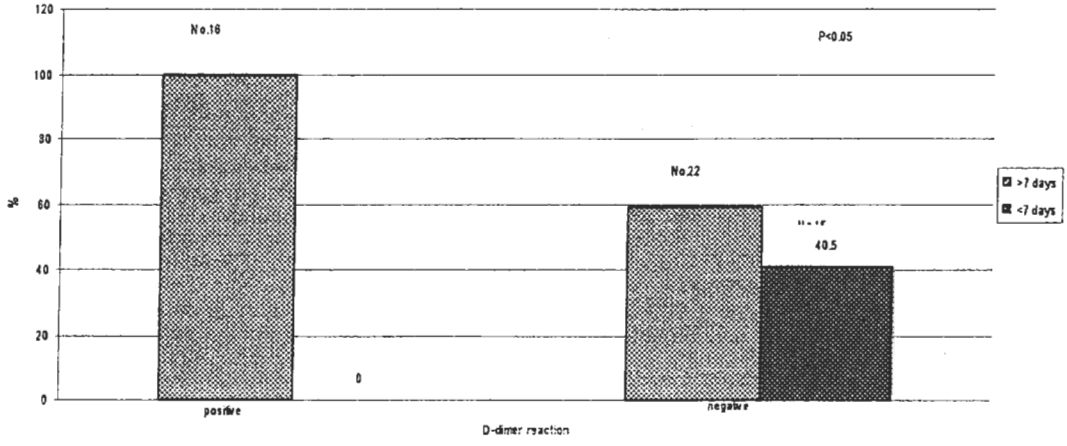
	Group I (No.16)		Group II (No.37)		Control (No.30)		P Value
	Range	X ±SD	Range	X ±SD	Range	X ±SD	
Plasma fibrinogen(g/L)	1.7-2.5	2.1±0.4	2.4-4	3.2±0.8	2.5-4.3	3.4±0.9	<0.05
Hb (g/L)	81-135	108±27	69-135	102±33	117-123	120±3	NS
Platelet count X 10^9/L	170-310	240±70	175-299	237±62	174-325	249±75	NS

During this study we identified 2 subgroups of patients in the studied group. Group 1, including 16 out of 53 (30.2%) with positive plasma D-dimer test (>0.5mg/ml), the normal range of D-dimer test is(<0.5mg/ml). The mean plasma fibrinogen levels was 2.1g/l with a range of (1.7-2.5g/L). the mean haemoglobin level was 108g/l with a range of 81-135g/L; as shown in table 1. Anaemia was seen in 9 out of 16 patients (56.2%) in group1.

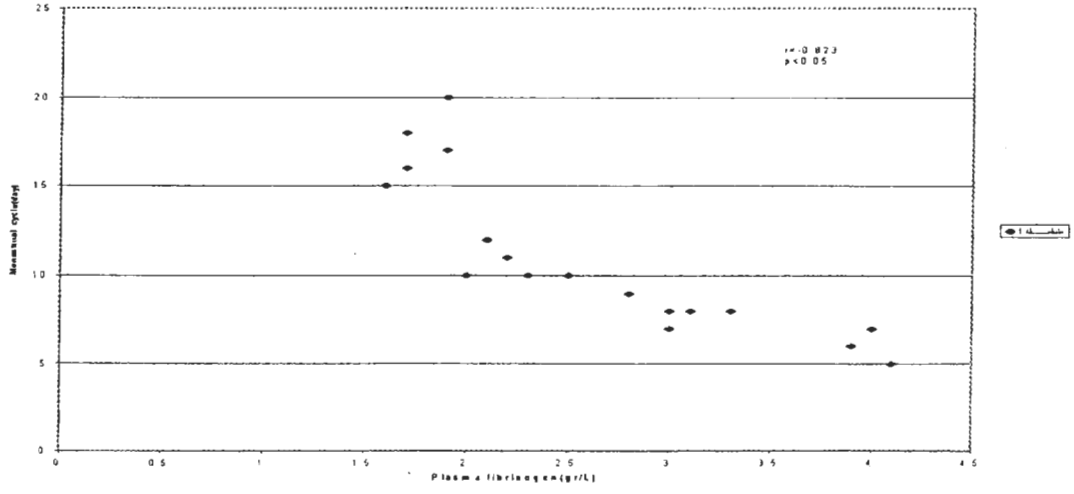
Group II included 37 out of 53 patients (69.8%) with negative plasma D-dimer test (<0.5mg/ml) and a mean plasma fibrinogen level of 3.2g/L and a range of (2.4-4g/L). The mean haemoglobin level was 102g/L with a range of (69-135g/L). Anaemia was seen in 21out of 37cases (56.7%). The D-dimer was significantly positive in patients with idiopathic menorrhagia compared to the control group with ($p<0.005$). The D-dimer test was negative in all women in control group. Positive D-dimer was significantly seen in those with prolonged duration of menstruations (>7days) compared to those with short duration of cycles with ($p<0.05$) as shown in (Figure1).

Plasma fibrinogen level was significantly lower in patients with positive D-dimer with ($p<0.05$) (Table 1). Significant negative correlation was found between plasma fibrinogen level and duration of menstrual cycle (Figure 2) ($P<0.05$).

Antifibrinolytic agent (tranexamic acid) was given to all patients, 15/16 (93%) of women responded to the treatment in group I, while the response in the group II was in 20/37 (54%). The drug was used for three cycles starting from the first day of the cycle and for 5days in a dose of 500mg three times per day.



Figure(1): *The significance of positive D-dimer reaction in patients with prolonged duration of menstrual cycle.*



Figure(2): *Correlation between plasma fibrinogen level and duration of menstrual cycle.*

DISCUSSION

In this study positive plasma D-dimer test (level >0.5mg/ml) was found in 16/53 (30.2%) of cases with idiopathic menorrhagia. The D-dimer is a marker of fibrinolysis, and has been mentioned in many studies[11,12]. Bisht et al mentioned that the fibrinolysis could be a cause of idiopathic menorrhagia, using the serum fibrin / fibrinogen degradation products (FDP) as a guide.

Positive plasma D-dimer test was more significantly seen in our patients with prolonged duration of the cycle (>7days) figure (1), positive correlation between duration of bleeding and FDP level was observed by others[6,13].

In the present study significantly lower plasma fibrinogen level was found in patients with positive plasma D-dimer reaction (group I) compared to both (group II) and the control group (table 1) ($p<0.05$), and this may be attributed to excessive fibrinolytic activity present in such cases. The significantly low plasma fibrinogen level found in those with long cycle indicates increased fibrinolysis in these patients (figure 2). Bleeding in group II may be due to increased fibrinolytic activity in uterus, secondary to plasminogen activator[3,14]. Such patients (group I and group II) are likely to be benefited with antifibrinolytic agents also as mentioned by others[11,12]. Antifibrinolytic agent reduced the menstrual loss by about 50%[4].

In our study we have 82.5% women with anaemia, and this was most probably due to the large amount of blood loss during menstruations.

CONCLUSIONS AND ECOMMENDATIONS

Increased fibrinolytic activity may cause idiopathic DUB, which could be assessed by D-dimer test and plasma fibrinogen assay.

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