Mild to moderate bleeding: diagnostic and therapeutic paths

Caterina Cenci,[1] Elena Silvestri,[2] Alberto Marchi,[1] Giacomo Emmi,[2] Domenico Prisco[2]

[1]Medical Pathology Department, Careggi University Hospital, Florence; [2]Experimental and Clinical Medicine Department, University of Florence, Florence, Italy

Abstract

We consider mild to moderate bleedings all bleeding events that do not meet the criteria proposed by the International Society of Thrombosis and Haemostasis (ISTH) for the definition of major bleeding. As regards the approach to the bleeding patient, the first step is undoubtedly an accurate collection of clinical history and overall physical examination. Then, the etiological diagnosis of a bleeding disorder uses a series of laboratory investigations, divided into first level tests, which are intended to identify the altered phase of the hemostatic process, and second level ones, *i.e.* more specific tests used if screening tests are negative or to better characterize the alteration identified by them. For the treatment of a bleeding disorder there are several approaches, all strictly dependent on the etiologic diagnosis of this disorder.

Introduction

We consider mild to moderate bleedings all bleeding events that do not meet the International Society of Thrombosis and Haemostasis (ISTH) criteria[1] according to which major bleeding is defined: i) fatal bleeding; and/or ii) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; and /or iii) bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

Differently from previous definitions, ISTH experts did not include in major bleeding *bleeding resulting in surgical intervention as a separate criterion as, if no other criteria for major bleeding have been satisfied, performance of surgical interventions will often be minor and not justify categorization as a major bleed*.[1] Thus, many bleedings resulting in surgical procedures have to be considered mild to moderate. Bleeding disorders defined as *mild to moderate* refer to those conditions in which there is an increased tendency to bleeding, in particular associated with trauma and surgery, but in which life-threatening bleeding does not generally occur. Therefore, the discrimination between normal and a pathological tendency to bleed is often challenging,[2] because most symptoms may occur in healthy subjects, but it is of pivotal importance to identify patients with hemostatic disorders who need investigations and specific treatments.

The International Society of Thrombosis and Haemostasis questionnaire

The first step of the approach to a bleeding patient is undoubtedly the collection of personal and family medical history as accurately as possible in order to ascertain the type of bleeding disorder and its characteristics, the age of onset of symptoms, the presence of similar events in other family members, the recent exposure to medications, the concomitant presence of other diseases. In this regard, some questionnaires that provide more effective criteria for the formulation of questions and the evaluation of the related answers have been produced. In particular, the ISTH questionnaire consists of two stages: the first is the collection of a bleeding history following encoded criteria (Table 1) and the second is the attribution of a predetermined value to each symptom based on its severity according to a *bleeding score* (Table 2). The use of such questionnaires is actually much debated as they are not applicable in all the conditions; however, they have been demonstrated to be effective in identifying, among patients with a probable bleeding diathesis, those with a real clinical problem that require further diagnostic investigations.[3] In particular, although the use of this *bleeding score* has been formally validated only for von Willebrand's disease patients but not for those with other bleeding disorders, a score greater than 3 in males and more than 5 in females can be considered highly suggestive of the real existence of a bleeding diathesis.[4]

Secondly, it should not be overlooked an accurate general physical examination that must include an assessment of the overall status (vital signs, state of the skin and mucous membranes, any associated sign, consciousness) and the search for specific patterns that may direct the physician to the correct diagnosis.[5] For example, the detection of petechiae can evoke the suspicion of thrombocytopenia, bleeding from the mucous membranes can orient towards the von Willebrand's disease or a pathology of platelets, while a muscular hematoma may point to a lack of coagulation factors.

The definitive diagnosis of a specific bleeding disorder also employs a series of laboratory tests, divided into first level tests (screening tests), which are intended to identify the altered phase of the haemostatic process, and second level tests, or more specific surveys useful in the case in which screening tests are normal or to better characterize the alteration(s) identified. In the case of altered results, it is necessary to evaluate the accuracy of data, which depends on a correct preparation and manipulation of the sample, and, in any case, confirm it with a repetition of the test on a new sample.

First level tests (Table 3)[6] include blood count with platelet count, bleeding time and/or the more recent platelet function analyzer (PFA)-100, which explore primary haemostasis, prothrombin time (PT), activated partial thromboplastin time (aPTT) and the dosage of fibrinogen, which explore the coagulation cascade. According to some, also the determination of AB0 blood group and the tests that explore liver function belong to first level tests, since it is known that group 0 subjects are more prone to develop a bleeding diathesis compared to subjects of other blood groups.[7] Moreover, given the high prevalence in the population of von Willebrand disease, many centers include the immunoassay of von Willebrand factor (VWF:Ag) associated with the specific assay of the VWF activity on platelet agglutination in the presence of risto-

Correspondence: Caterina Cenci, Medical Pathology Department, Careggi University Hospital, largo Brambilla 3, 50134 Florence, Italy.
Tel. +39.347.1662592 - Fax: +39.055.794.6455.
E-mail: caterinacenci@gmail.com

Key words: mild bleeding, moderate bleeding, ISTH questionnaire.

Contributions: the authors contributed equally.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 15 March 2013.
Revision received: 2 September 2013.
Accepted for publication: 5 September 2013.

Emergency Care Journal 2013; 9:e22
doi:10.4081/ecj.2013.e22

cetin (ristocetinic cofactor activity, VWF:RCo) and factor VIII coagulant activity (FVIII:C) in the group of first level tests.

Second level tests (Table 4) include mixing tests, platelet aggregation test, the dosage of individual coagulation factors, and possibly the tests exploring the fibrinolytic cascade. In the case of a patient with bleeding diathesis, first level tests help to determine whether the defect is to be referred to primary haemostasis (vascular phase/platelets) or secondary haemostasis (coagulation phase). Platelet count allows to identify a thrombocytopenia while, in the case of platelet normal values, the PFA-100, able to reproduce in vitro platelet adhesion and aggregation, and the much more operator-dependent bleeding time according to Mielke method are able to identify the existence of a platelet dysfunction or von Willebrand disease. In the case of positive results of these tests, it is indicated to start specific diagnostics for von Willebrand disease, the most common bleeding disorder, and to carry out, if this diagnosis is excluded, platelet aggregation tests. It should be noted that the characterization of a congenital thrombocytopathy requires highly specialized centers; moreover, we must remember the need for a careful drug history in the interpretation of an altered result of tests exploring platelet function.

PT is defined as the time in seconds an aliquot of platelet-poor plasma takes to clot following the addition of an extract of tissue factor of human or animal origin (thromboplastin) and calcium ions at 37°C. This test explores the extrinsic and common pathway of coagulation and it is prolonged in case of factor II, V, VII, X, and fibrinogen deficiency, as well as during treatment with antagonists of vitamin K. It should be noted that the test is commonly altered in advanced liver disease and vitamin K deficiencies. aPTT, instead, is the time in seconds an aliquot of platelet-poor plasma takes to clot following the addition of an activator of the contact phase (kaolin, ellagic acid, silica, etc.), of phospholipids and calcium ions at 37°C. This test explores the intrinsic and common coagulation pathway and it is prolonged in case of factors II, V, VIII, IX, X, XI and fibrinogen deficiency as well as during therapy with unfractionated heparin, and often with antagonists of vitamin K. The presence of antiphospholipid antibodies and factor XII

Table 1. The International Society of Thrombosis and Haemostasis questionnaire.

Symptom	Relevant features	Questions
Epistaxis	Frequent (at least once a week); Duration>5'; Not only pre-puberal; Complicated	How many episodes/year? How long they last? Are they spontaneous or after drug assumption? What was the age of maximum frequency? Did they require medical attention? If yes, please specify
Cutaneous symptoms	Spontaneous bruising or hematoma>3 cm	Which kind of manifestation? Where? After trauma? If yes, which kind of trauma? Did they require medical attention? If yes, please specify
Bleeding from minor wounds	Duration>5' At least 1 episode/year due to superficial cuts	How many episodes/year? How long they last? Did they require medical attention? If yes, please specify
Bleeding in the oral cavity	Spontaneous gingival bleeding lasting>1' characterized by the presence of blood in the sputum or resulting from brushing; Bleeding of labial, buccal, or lingual mucosa>5' or that causes swelling of the tongue or mouth; Any bleeding after dental eruption that requires medical attention	Where? In which occasion? Did they require medical attention? If yes, please specify
Gastrointestinal bleeding	Any	How many episodes/year? Which kind of manifestation? Is it associated to local diseases? Did they require medical attention? If yes, please specify
Post-dental extraction bleeding	Any bleeding that occurs during or post dental extraction that complicated it	What is the ratio between number of dental extraction and those complicated? At what age and what type of tooth? kind of therapeutic measure was needed?
Post-surgery bleeding	Any bleeding considered excessive by the surgeon or that has determined a delay in the discharge from the hospital delayed or that made it necessary any supportive treatment	What is the ratio between total number of surgery and those complicated? What is the type of surgery? What kind of therapeutic measure was needed?
Menorrhagia	None	What is the duration of average menstruation (days)? What is the duration of heavy menstruation (days)? What is the age of onset and when has it reached the maximum intensity? Did it require medical attention? If yes, please specify
Post-partum hemorrhage	None	What is the ratio between number of deliveries and those complicated? What kind of therapeutic measure was needed?
Muscle ematoma or hemarthrosis	None	Where? Spontaneous or traumatic?

deficiency explain those cases in which aPTT is prolonged in the absence of a hemorrhagic syndrome. PT and aPTT, therefore, investigate the function of several coagulation factors while each one is sensitive to a more limited group of factors. Their values allow not only to confirm or rule out an alteration of secondary haemostasis but also to orient toward the possible defect: for example, the isolated prolongation of PT is suggestive for factor VII deficiency, while the alteration of both tests occurs in factor II, V, X and fibrinogen deficiency as well as during antagonists of vitamin K treatment, in advanced liver disease and disseminated intravascular coagulation. The deficiency of one or more factors or the presence of an inhibitor of coagulation is determined by repeating the test on a mixture prepared with the patient plasma and a normal plasma in a 1:1 ratio. If the coagulation time performed on the mixture results closer to that of normal plasma we can conclude for a factor deficiency and we will proceed with the dosage of the individual related coagulation factors; instead, if the clotting time of the mixture turns out to be closer to that obtained on patient plasma we will likely be in the presence of an inhibitor of coagulation.

Another situation, although not very frequent, is the presence of an abnormal fibrinogen (dysfibrinogenemia)[8] in patient plasma and in this case PT and aPTT tests are not very sensitive. This condition, whose consequence can be both a bleeding or a thrombotic event (depending on the type of defect), is diagnosed thanks to the functional and immunological assay of fibrinogen or using the thrombin time and the reptilase time. These last two tests directly explore the conversion reaction of fibrinogen to fibrin: thrombin time, however, is also affected by the therapy with heparin so, by using the two tests together, we can identify those situations in which both tests are altered due to a dysfibrinogenemia.

If the results of the tests are normal, but the patient's medical history is positive for bleeding, the dosage of factor XIII, whose deficiency can lead to a rare hemorrhagic syndrome, and the exploration of the fibrinolytic system with the dosages of antiplasmin, tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI-1),[9,10] may be useful.

Principles of therapy

It is difficult to give an appropriate treatment algorithm for patients with mild to moderate bleeding disorders since the treatment depends critically on the specific diagnosis and it has been shown by a recent study that in 54% of those patients with family and personal history of mucocutaneous bleeding a cause cannot be identified.[11] In addition, before starting a treatment a balance between its risks and benefits should be evaluated: in fact, on one hand, the use of specific drugs active on the haemostatic cascade is able to block the process by reducing hemorrhagic complications, but, on the other hand, these drugs may increase the risk of thrombotic events.[11] In case of bleeding during antiplatelet or anticoagulant therapy, the first decision is to stop the antithrombotic drug. For the treatment of bleeding disorders, in addition to the use of concentrates of coagulation factors in the case of specific factors deficiencies, a possible option are the inhibitors of the fibrinolytic cascade such as tranexamic acid that is normally used with success both in the prevention of bleeding events in patients at risk before surgical procedures, and in the therapy of acute mucocutaneous bleeding (for example in case of menorrhagia).[12,13] It is also known that desmopressin, a synthetic analogue of vasopressin, is effective in the prevention of bleeding in patients with haemophilia A and type 1 von Willebrand disease since it is able to raise by 3-4 times the plasma concentrations of von Willebrand factor and factor VIII. Although there have been few reports of serious side effects, the drug is contraindicated in patients under the age of 2 years, for the risk of hyponatremia, in adults with symptomatic atherosclerosis[14] and in women with menorrhagia; in the latter situation desmopressin is used as second-line therapy or in addition to an anti-fibri-

Table 2. Bleeding score.

Symptom	Score
Epistaxis	0=no or trivial 1=present 2=packing or cauterization 3=blood transfusion or replacement therapy
Cutaneous	0=no or trivial 1=petechiae or bruises 2=haematomas 3=consultation
Bleeding from minor wounds	0=no or trivial 1=present 2=consultation 3=surgical haemostasis
Oral cavity	0=no or trivial 1=present 2=consultation only 3=surgical haemostasis or blood transfusion
Gastrointestinal bleeding	0=no or trivial 1=present 2=consultation only 3=surgery/ blood transfusion
Post-partum haemorrage	0=no or trivial 1=present, iron therapy 2=blood transfusion, dilatation and curettage, suturing 3=hysterectomy
Muscle haematomas or haemarthrosis	0=no or trivial 1=present 2=consultation only 3=blood transfusion, surgery
Tooth extraction	0=no or trivial 1=present 2=suturing or packing 3=blood transfusion
Surgery	0=no or trivial 1=present 2=suturing or resurgery 3=blood transfusion
Menorrhagia	0=no or trivial 1=present 2=consultation, contraceptive pill use, iron therapy 3=blood transfusion, hysterectomy, dilatation and curettage

Table 3. First level tests (modified from De Moerloose *et al.*, 2009).

Basal hematocrit and platelet count
Bleeding time/PFA-100
PT
aPTT
Fibrinogen
VWF:Ag, VWF:RCo, FVIII:C

PFA, platelet function analyzer; PT, prothrombin time; aPTT, activated partial thromboplastin time; VWF:Ag, immunoassay of von Willebrand factor; VWF:RCo, assay of the VWF activity on platelet agglutination in the presence of ristocetinic cofactor activity; FVIII:C, factor VIII coagulant activity.

Table 4. Second level tests (modified from De Moerloose *et al.*, 2009).

Mixing tests
Specific coagulation factors
Platelet aggregation test
Factor XIII
Alpha2-antiplasmin*

*A more extensive exploration of fibrinolytic system is not usually recommended except for in specialized centers with specific expertise.

nolytic drug in case of non-remission of haemorrhagic symptoms.[15]

Conclusions

One of the challenges of the coming years will be the management of bleeding events during therapy with the new oral anticoagulants. It must be said, however, that in the context of mild to moderate bleeding the management will be relatively easy and based only on the discontinuation of treatment thanks to the short half-life of these drugs.

References

1. Schulman S, Kearon C. Definition of major bleeding in clinical investigations and antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.
2. Rodeghiero F, Tosetto A, Castaman G. How to estimate bleeding risk in mild bleeding disorders. J Thromb Haemost 2007;5:157-66.
3. Sramek A, Eikenboom JC, Briet E, et al. Usefulness of patient interview in bleeding disorders. Arch Intern Med 1995;155:1409-15.
4. Rodeghiero F, Castaman G, Tosetto A, et al. The discriminant power of bleeding history for the diagnosis of von Willebrand disease type 1: an international, multicenter study. J Thromb Haemost 2005;3:2619-26.
5. Girolami A, Luzzatto G, Varvarikis C, et al. Main clinical manifestations of a bleeding diathesis: an often disregarded aspect of medical and surgical history taking. Haemophilia 2005;11:193-202.
6. De Moerloose P, Levrat E, Fontana P, Boehlen F. Diagnosis of mild bleeding disorders. Swiss Med Wkly 2009;139:327-32.
7. O'Donnell J, Laffan MA. The relationship between ABO histo-blood group, factor VIII and von Willebrand factor. Transfus Med Rev 2001;11:343-51.
8. Rocha E, Paramo JA, Aranda A, et al. Congenital dysfibrinogenemias. A review. Res Clin Lab 1985;15:205-29.
9. Tripodi A. [Linee guida per lo screening dei pazienti in emergenza emorragica]. [Article in Italian]. Available from: http://www.sisetonline.com/lineeguida/all_pdf/emergenza1999.pdf
10. Tripodi A. [Linee guida per lo screening dei pazienti con sospetto difetto emorragico congenito]. [Article in Italian]. Available from: http://www.sisetonline.com/lineeguida/all_pdf/difetto.pdf
11. Quiroga T, Goycoolea M, Munoz B, et al. Template bleeding time and PFA-100 have low sensitivity to screen patients with hereditary mucocutaneous hemorrhages: comparative study in 148 patients. J Thromb Haemost 2004;2:892-8.
12. Hayward CPM. Diagnosis and management of mild bleeding disorders. Hematology Am Soc Hematol Educ Program 2005:423-8. Available from: http://asheducationbook.hematologylibrary.org/content/2005/1/423.full.pdf
13. Henry DA, Moxey AJ, Carless PA, et al. Anti-fibrinolytic use for minimising perioperative allogenic bllod transfusion. Cochrane Db Syst Rev 2001;1:CD001886.
14. Carless PA, Henry DA, Moxey AJ, et al. Desmopressin for minimising perioperative allogenic blood transfusion. Cochrane Db Syst Rev 2004;1:CD001884.
15. Lenthagen S. Desmopressin in the treatment of women's bleeding disorders. Haemophilia 1999;5:233-7.