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REPORTS OF ORIGINAL INVESTIGATIONS

Preoperative hemostatic assessment: a new and simple bleeding questionnaire

Évaluation préopératoire de l'hémostase: un nouveau questionnaire simple sur le saignement

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Abstract

Purpose *Current recommendations for the assessment of the risk of perioperative bleeding limit coagulation testing to patients with a personal and/or family history of bleeding. As no simple preoperative screening questionnaire is currently available, we assessed the performance of a novel screening questionnaire for its ability to detect bleeding disorders.*

Methods *A dichotomized, seven-point questionnaire named HEMSTOP (Hematoma, hEmorrhage, Menorrhagia, Surgery, Tooth extraction, Obstetrics, Parents) was applied to three groups of subjects: patients referred to hemostasis specialists for bleeding symptoms for whom any kind of perioperative hemostatic precautions were subsequently recommended ($n = 38$); patients referred to hemostasis specialists for whom precautions were not required ($n = 75$); healthy volunteers ($n = 70$). We calculated the sensitivity and specificity of HEMSTOP scores and compared them with the discriminative performances of standard blood coagulation assays (prothrombin time, activated partial thromboplastin time).*

Results *Patients requiring perioperative hemostatic precautions had greater median [interquartile range] HEMSTOP scores (2 [2-3]) than patients not requiring precautions (1 [1-2]) and healthy controls (0 [0-0]); $P < 0.001$. A HEMSTOP score ≥ 2 had a specificity of 98.6% [95% confidence interval (CI), 92.3 to 100] and a sensitivity of 89.5% (95% CI, 75.2 to 97.1). The 26.3% (95% CI, 13.4 to 43.1) sensitivity of the standard coagulation times was much lower.*

Conclusion *The HEMSTOP score discriminates patients at an elevated risk for bleeding with recommended perioperative precautions from those without such recommendations as well as from healthy participants. Further evaluation of the HEMSTOP score is required for a better evaluation of its definitive usefulness to predict the risk of perioperative bleeding.*

Résumé

Objectif *Les recommandations actuelles concernant l'évaluation du risque hémorragique périopératoire ne préconisent des tests de coagulation que chez les patients présentant des antécédents personnels et/ou familiaux de saignement . Comme il n'existe, à l'heure actuelle, aucun questionnaire simple de dépistage préopératoire, nous avons évalué la performance d'un questionnaire de dépistage innovant afin de déterminer sa capacité à détecter les troubles de l'hémostase à risque hémorragique.*

Méthode *Un questionnaire binaire en sept points, baptisé HEMSTOP (pour Hematoma, hEmorrhage, Menorrhagia, Surgery, Tooth extraction, Obstetrics, Parents, soit hématome, hémorragie, ménorragie, chirurgie, extraction dentaire, obstétrique, famille) a été appliqué à trois groupes de patients: patients référés à des spécialistes de l'hémostase pour diathèse hémorragique et pour lesquels des précautions hémostatiques périopératoires étaient*

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prescrites par la suite (n = 38); patients référés à des spécialistes de l'hémostase mais pour lesquels aucune précaution n'était requise (n = 75); volontaires sains (n = 70). Nous avons calculé la sensibilité et la spécificité de notre questionnaire HEMSTOP et les avons comparées aux performances discriminatives des tests de coagulation sanguine standard (temps de prothrombine, temps de thromboplastine partielle activée).

Résultats *Les patients nécessitant des précautions hémostatiques périopératoires avaient des scores médians plus élevés [écart interquartile] au HEMSTOP (2 [2-3]) que les patients ne nécessitant pas de précautions (1 [1-2]) et les témoins sains (0 [0-0]); P < 0,001. Un score HEMSTOP ≥ 2 avait une spécificité de 98,6 % [intervalle de confiance (IC) 95 %, 92,3 à 100] et une sensibilité de 89,5 % (IC 95 %, 75,2 à 97,1). La sensibilité à 26,3 % (IC 95 %, 13,4 à 43,1) des temps de coagulation standard était beaucoup plus basse.*

Conclusion *Le score HEMSTOP différencie les patients à risque hémorragique périopératoire élevé pour lesquels des précautions sont recommandées de ceux ne nécessitant pas de telles précautions ainsi que des participants sains. Une évaluation prospective du score HEMSTOP est nécessaire afin de mieux évaluer sa véritable utilité pour prédire le risque de saignement périopératoire.*

The purpose for the detection of bleeding disorders during the preanesthetic evaluation is to prevent perioperative hemorrhagic complications through appropriate medical management. An undetected hemostatic disorder may result in excessive bleeding during and/or following surgery. Contrary to acquired disorders, the prevalence of inherited coagulation disorders and platelet dysfunctions, is much less common in the general population. In patients with no hemorrhagic symptoms, these diseases appear to be very rare, approximately one in 40,000 patients.[1] Acquired dysfunctions are the most frequent disorders, often due to targeted medical treatment, e.g., antiplatelet therapy and oral anticoagulation. Indiscriminate coagulation tests are still widely ordered prior to surgery, although these have limited sensitivity and specificity as well as poor positive and negative predictive values for bleeding.[2-4] Over the last decade, various anesthesiology and hematology societies have published guidelines regarding preoperative hemostatic evaluation.[5-7] These recommend that, prior to invasive procedures, the risk of bleeding should be assessed using personal and family bleeding histories in addition to a physical examination. However, an inadequately structured bleeding history is a poor predictor of perioperative hemorrhage as it can either under- or overestimate symptoms.[8]

Many questionnaires have been proposed,[9-14] but none of these have been validated as a predictor of the risk of perioperative bleeding. There are well-developed and validated questionnaires and bleeding scores[15-17] for identifying patients, even children,[18-20] who are suspected of von Willebrand disease (vWD) and require laboratory evaluation. These bleeding assessment tools may also be used for the evaluation of patients with suspected mild bleeding disorders.[21-23] The purpose of the present study was to generate and evaluate a rapid and simple bleeding questionnaire for identifying patients with an undiagnosed bleeding tendency requiring specific precautions and/or prophylactic treatment before invasive procedures. We termed the questionnaire HEMSTOP, which is the mnemonic acronym formed from **H**ematoma, h**E**morrhage, **M**enorrhagia, **S**urgery, **T**ooth extraction, **O**bstetrics, **P**arents. In developing the questionnaire, we were not concerned with the bleeding risk associated with the surgical procedure *per se*, ongoing medications, or any known pathological state potentially interfering with hemostasis, e.g., hepatic disease.

Methods

This observational study compared the HEMSTOP questionnaire scores of three groups of subjects. It was retrospectively applied to patients with bleeding symptoms and an elevated bleeding risk for whom perioperative precautions were recommended and to patients with some bleeding symptoms but without an identified bleeding risk and thus without recommended perioperative precautions, and was prospectively applied to healthy subjects (controls). The Geneva University Hospitals' Central Ethics Committee approved this study (n° 11-081R), and waived the requirement for written informed consent for the retrospective part of the study. All control subjects participating in the prospective portion provided written informed consent.

Generation of the HEMSTOP questionnaire

We initially performed a literature review to derive a bleeding questionnaire from empirical evidence. The symptoms typically linked with vWD—the most frequently inherited bleeding disorder—are excessive bleeding after surgery and cutaneous bleeding (e.g., ecchymosis or bruising). Conversely, the diagnosis of vWD is very unlikely in the absence of excessive bleeding after tooth extraction.[15] Other symptoms, such as epistaxis, prolonged bleeding after minor wounds, bleeding gums, gastrointestinal bleeding, hemarthrosis,

muscle hematoma, and intracranial hematoma, are less discriminating.[16,19,24] Heavy menstruation is a common and non-specific complaint among young patients, reported by up to 35% of women.[25] Nevertheless, inherited bleeding disorders (mostly vWD and platelet dysfunctions) are frequently diagnosed in females when they are referred for hemostasis investigation by a gynecologist for investigation of menorrhagia.[26] In such cases, 25% of patients also experience a postpartum hemorrhage.[27]

The HEMSTOP questionnaire was then derived further from a consensus reached by a group of anesthesiologists and hemostasis specialists. This group was composed of three anesthesiologists and five hemostasis specialists in academic practice from various geographic areas of France and from Geneva, Switzerland (see Acknowledgements). Seven items related to hematoma, unspecified bleeding, menorrhagia, surgery, dental extraction, postpartum hemorrhage, and family history were retained from the initial questionnaire (above).

The HEMSTOP questionnaire contains five questions relevant to all patients as well as two questions specific to females (Table 1). Binary questions were chosen to make the questionnaire unambiguous and simple to administer. Questions focused on symptoms requiring a medical consultation or a specific treatment. Each positive answer scores "1"; each negative answer scores "0".

Definition of groups

Three groups of subjects were *a priori* defined: patients referred to the hemostasis clinic of a tertiary centre for bleeding symptoms and for whom any kind of perioperative hemostatic prophylaxis or precaution was recommended, patients referred to the same hemostasis clinic because of bleeding symptoms but for whom precautions were not required, and healthy subjects with no identified bleeding risk (controls).

In the present study, a patient was considered as *requiring precautions* if a hemostatic investigation diagnosed a bleeding disorder with recommended prophylaxis prior to surgery, e.g., preoperative administration of desmopressin, coagulation factor concentrates, platelets. When the investigations could not precisely identify a hemostatic disorder, but the clinical bleeding symptoms were disturbing enough to require precautions (e.g., coagulation factors ready to order) in case of an invasive procedure, patients were also categorized as *requiring precautions* due to the perceived elevated risk of perioperative bleeding. Patients were considered as *not requiring precautions* if tests results showed no relevant hemostatic disorder and the bleeding symptoms were not sufficiently ominous to warrant precautions prior to surgery.

Controls were prospectively recruited from hospital medical and non-medical staff. They were considered eligible for the study if they were in general good health, were never referred for a hemostatic evaluation because of bleeding symptoms, and were not receiving medications that could potentially interfere with hemostasis, e.g., ongoing anticoagulant or antiplatelet therapy including low-dose acetylsalicylic acid. Laboratory screening was not performed as they were assumed to be unaffected by any hemostatic disorder.

Investigations in the hemostasis clinic

For patients referred to the hemostasis clinic, a personal and family bleeding history was carefully taken with a bleeding score table proposed by Tosetto *et al.*[16] For females, quantification of menstruation was systematically assessed using a pictorial chart method.[28] Except in cases of a positive familial hemostatic defect screening, patients referred for a hemostatic evaluation were first tested for prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, platelet count, factor VIII activity, von Willebrand ristocetin cofactor and PFA-100® (platelet function analyzer) closure times using both collagen/epinephrine and collagen/ADP cartridges. According to the results, additional tests were performed at the hemostasis specialist's discretion, including characterization of vWD, coagulation factors including factor XIII, platelet aggregation tests, platelet secretion tests, euglobulin lysis time, and antiplasmin level.

Calculation of the HEMSTOP score

We accessed the medical charts of all patients referred by their physician (e.g., general practitioner, gynecologist, and surgeon) to the Division of Angiology and Hemostasis at Geneva University Hospitals from January 2009 to February 2011 because of spontaneous or post-interventional bleeding, and we then retrospectively calculated the HEMSTOP scores using the information contained in the charts. There was a wide range of bleeding histories among these patients, with some sustaining a bleeding disorder that was subsequently diagnosed. All medical charts contained a precise and exhaustive bleeding history, a bleeding score table, and a pictorial chart for quantification of menstrual blood loss. One investigator calculated the HEMSTOP scores while blinded to the final diagnoses. The investigator first extracted the bleeding score table proposed by Tosetto *et al.*[16] from the medical records and scored the HEMSTOP items—except for the familial medical history (gleaned from the relevant section of the medical chart). The investigator then compiled the results of laboratory investigations onto an electronic database. Finally, the investigator accessed the

Table 1 HEMSTOP Questionnaire

1. Have you ever consulted a doctor or received treatment for prolonged or unusual bleeding (such as nosebleeds, minor wounds)?
2. Do you experience bruises/hematomas larger than 2 cm without trauma or severe bruising after minor trauma?
3. After a tooth extraction, have you ever experienced prolonged bleeding requiring medical/dental consultation?
4. Have you experienced excessive bleeding during or after surgery?
5. Is there anyone in your family who suffers from a coagulation disease (such as hemophilia, von Willebrand disease, etc.)?
For females:
6. Have you ever consulted a doctor or received a treatment for heavy or prolonged menstrual periods (contraceptive pill, iron, etc.)?
7. Did you experience prolonged or excessive bleeding after delivery?

HEMSTOP = Hematoma, hEmorrhage, Menorrhagia, Surgery, Tooth extraction, Obstetrics, Parents

Table 2 Demographic characteristics and qualitative analysis of symptoms among patients *requiring* and *not requiring precautions* and *controls*

	Requiring precautions $n = 38$	Not requiring precautions $n = 75$	Controls $n = 70$
Demographic characteristics			
Age	40 (16)	41 (16.5)	41 (10)
Male	7 (18.4%)	18 (24%)	40 (57.1%)
Symptoms (as defined in questionnaire)			
Prolonged/unusual bleeding	24 (63.2%)*†	14 (18.7%)†	0 (0%)
Bruises/hematomas	15 (39.5%)†	18 (24.0%)†	3 (4.3%)
Bleeding after tooth extraction	11 (28.9%)*†	5 (6.7%)	0 (0%)
Postoperative bleeding	19 (50.0%)*†	22 (29.3%)†	1 (1.4%)
Relatives with hemostatic disorder	5 (13.2%)†	10 (13.3%)†	1 (1.4%)
Menorrhagia	15/31 females (48.4%)†	28/57 females (49.1%)†	5/30 females (16.7%)
Postpartum hemorrhage	11/31 females (35.5%)*†	8/57 females (14.0%)	1/30 females (3.3%)
Hemostatic screening tests			
Prolonged PT	1 (2.6%)	1 (1.3%)	NA
Prolonged aPTT	10 (26.3%)	2 (2.7%)	NA
Bleeding disorder			
Type 1 von Willebrand	14 (36.8%)	0 (0%)	NA
Platelet dysfunctions	12 (31.6%)	0 (0%)	NA
Type 2 von Willebrand	2 (5.3%)	0 (0%)	NA
Type 1 von Willebrand plus factor XI deficiency	1 (2.6%)	0 (0%)	NA
Mild hemophilia A	1 (2.6%)	0 (0%)	NA
Other minor disorders	5 (13.2%)	0 (0%)	NA
Acquired hemostatic disorder	3 (7.9%)	0 (0%)	NA

Data are number of patients (%) or mean (SD)

aPTT = activated partial thromboplastin time; NA = not appropriate; PT = prothrombin time. * $P < 0.05$ *vs not requiring precautions*; † $P < 0.05$ *vs* controls

entire electronic medical chart to extract the conclusions (diagnosis and precautions if any). For control subjects, the HEMSTOP scores were prospectively calculated from a self-administered questionnaire.

Statistical analysis

The HEMSTOP scores are expressed as median [interquartile range (IQR)]. Statistical analysis comparing the three groups of subjects (*requiring precautions, not requiring precautions, controls)* was done using the Kruskal-Wallis test, followed by Dunn's multiple comparison tests. Proportions were compared by the Fisher's exact test. Sensitivity (the test can correctly identify those patients with the disease) and specificity (the test can correctly identify those patients without the disease) were calculated among patients *requiring precautions* and *controls*, respectively, and positive and negative predictive values (PPV, NPV)

Table 3 HEMSTOP score in patients *requiring* and *not requiring precautions* before an invasive procedure and *controls*

	Requiring precautions $n = 38$	Not requiring precautions $n = 75$	Control subjects $n = 70$	
HEMSTOP score (positive answers)				
0	0	3 (4%)	60 (85.7%)	For cut-off ≥ 2
1	4 (10.5%)	49 (65.3%)	9 (12.9%)	Sensitivity = 89.5% (75.2 to 97.1)
2	18 (47.4%)	15.0 (20%)	1 (1.4%)	Specificity = 98.6% (92.3 to 100)
3	9 (23.7%)	6 (8.0%)	-	
4	4 (10.5%)	2 (2.7%)	-	
5	1 (2.6%)	-	-	
6	2 (5.3%)	-	-	
7	-	-	-	
Hemostatic screening tests				
Prolonged PT	1 (2.6%)	1 (1.3%)	NA	Sensitivity of both together = 26.3% (13.4 to 43.1)
Prolonged aPTT	10 (26.3%)	2 (2.7%)	NA	Theoretical specificity (derived from normal definition) = 97.5%

Data are number of patients (%), unless for sensitivity and specificity, % (95% confidence interval)

aPTT = activated partial thromboplastin time; HEMSTOP = Hematoma, hEmorrhage, Menorrhagia, Surgery, Tooth extraction, Obstetrics, Parents; NA = not appropriate; PT = prothrombin time

were computed based on the prevalence of a constitutional bleeding disorder of 1% (close to vWD prevalence). All analyses were conducted on Stata (STATA Corp., College Station, TX, USA). All reported *P* values are two-sided.

Results

Patient characteristics

From January 2009 to February 2011, 166 patients were referred to the Hemostasis Unit because of bleeding symptoms. Exclusion criteria were patients with a previously diagnosed bleeding disorder presenting for follow-up or those whose laboratory tests had not been completed ($n = 53$). Thirty-eight of the 113 patients remaining for further analysis were classified as *requiring precautions* and 75 were classified as *not requiring precautions*. An additional 70 individuals were recruited as controls. The demographic characteristics of all study subjects are given in Table 2.

Bleeding symptoms in patients not requiring precautions

Of the 75 patients not requiring precautions, the most frequent symptom was menorrhagia in females (49.1%) (Table 2). Excessive postoperative bleeding and bruises/hematomas were reported in 29.3% and 24% of patients, respectively. Other minor symptoms not requiring medical consultation were also reported, including bleeding gums and prolonged bleeding after minor wounds. The majority of these patients (64%) experienced at least two invasive procedures (tooth extraction and/or surgery) without excessive bleeding.

Among these 75 patients, two had a prolonged aPTT, and one had a slightly prolonged PT; platelet counts were all within the normal range. Based on a reassuring bleeding history, four patients had no further laboratory testing. The remaining 71 patients were tested for fibrinogen level, platelet count, factor VIII activity, von Willebrand ristocetin cofactor, and PFA-100 closure times, and all results were within the normal range. In one-third of these patients, additional tests were performed at the hemostasis specialist's discretion, e.g., characterization of vWD, coagulation factors including factor XIII, platelet aggregation tests, platelet secretion tests, euglobulin lysis time, and antiplasmin level. The final diagnosis for this group of patients was the absence of any bleeding disorder; therefore, perioperative bleeding precautions were not indicated.

Bleeding symptoms in patients requiring precautions

Of the 38 patients *requiring precautions*, the most frequent symptoms were bleeding events requiring medical consultation or specific treatment (63.2%) and excessive bleeding after invasive procedures—i.e., postoperative bleeding (50%) and bleeding after tooth extraction (29%)

or after delivery (35.5% of females). Among females, 48.4% also reported menorrhagia. Bruises/hematomas were reported in 39.5% of patients (Table 2). Compared with patients *not requiring precautions*, those *requiring precautions* experienced more frequent prolonged/unusual bleeding, bleeding after tooth extraction, postoperative bleeding, or postpartum hemorrhage.

Regarding standard laboratory testing, only one patient had a prolonged PT and aPTT, and high doses of acenocoumarol were administered to this patient by her family. Among the 37 other patients, nine (24%) had a prolonged aPTT. Platelet counts of all 38 patients were in the normal range. Diagnoses were made on the basis of other biological tests: factor VIII activity, von Willebrand ristocetin cofactor, and PFA-100 closure times. Other analyses, such as characterization of vWD, coagulation factors including factor XIII, platelet aggregation tests, platelet secretion tests, euglobulin lysis time, and antiplasmin level, were performed at the physician's discretion. Of the 38 patients *requiring precautions*, the most common diagnosis was, unsurprisingly, type 1 vWD (n = 14) (Table 2). The second most common diagnosis was platelet dysfunction (n = 12). No known hemostatic disorder could be identified for five patients with a bleeding phenotype. Nevertheless, due to the importance of bleeding symptoms, the physician concluded that other minor disorders could not be ruled out and recommended precautions in case of surgery. Three patients were diagnosed with an acquired hemostatic disorder (acquired type 2 vWD, acquired hemophilia A, and acenocoumarol intoxication). Additionally, two patients were diagnosed with type 2 vWD, one with type 1 vWD and factor XI deficiency, and another with mild hemophilia A.

The HEMSTOP score

The median [IQR] (range) HEMSTOP scores for patients *requiring precautions, not requiring precautions*, and *controls* were 2 [2-3] (1-6) *vs* 1[1-2] (0-4) *vs* 0 [0-0] (0-2), respectively (Table 3). The scores between the three groups were statistically different ($P < 0.001$). Between-group scores were also different ($P < 0.001$), as indicated in the Figure. The median HEMSTOP score was significantly higher in symptomatic patients *requiring precautions* than in patients *not requiring precautions* ($P < 0.001$). Among symptomatic patients *not requiring precautions*, 70% had a HEMSTOP score lower than two, and 30% had a score equal to or greater than two. The HEMSTOP score for the majority (86%) of controls was 0; a few (13%) had a score of one, and only 1% had a score of 2. Importantly, no control subjects had a score greater than two.

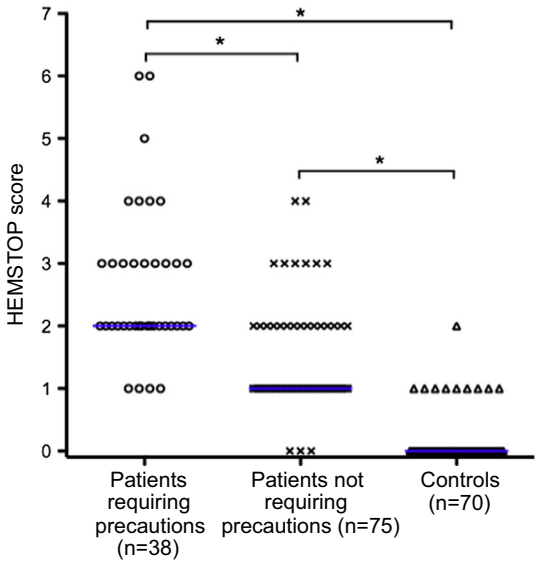

Figure HEMSTOP (Hematoma, hEmorrhage, Menorrhagia, Surgery, Tooth extraction, Obstetrics, Parents) score according to subject group. The HEMSTOP score for each subject is shown, and the horizontal line indicates the median score for each group. An overall comparison using the Kruskal-Wallis test indicated significant differences between groups ($P < 0.0001$), with significant between-group differences as indicated (Dunn's multiple comparison tests *$P < 0.001$)

The four patients requiring precautions but who scored only one positive answer on the HEMSTOP questionnaire (score = 1) warrant consideration. One of these patients was a 60-yr-old male suffering from a myeloma and diagnosed with an acquired type 2 vWD (von Willebrand factor ristocetin cofactor assay [vWF:RCo] = 18%; von Willebrand factor antigen [vWF:Ag] = 56%). He never experienced an unusual bleeding history (even after tooth extractions), but subsequently experienced a postoperative hemorrhage after a thoracotomy. Another patient was a young male with a very mild type 1 vWD (vWF:RCo = 37%; vWF:Ag = 44%; collagen-binding assay [CBA] = 39%, O blood group) who reported only epistaxis (multiple tooth extractions without problems). A young 17-yr-old female was diagnosed with a platelet dysfunction (thromboxane A_2 receptor defect). She reported epistaxis (but no consultation for this condition) and menorrhagia causing anemia that required iron therapy. She never had surgery or a tooth extraction. The last patient was also a young 17-yr-old female with no history of surgery or tooth extraction who was anemic because of menorrhagia. A diagnosis of type 1 vWD was considered possible, although not certain (vWF:RCo = 46%; vWF:Ag = 65%). Routine coagulation tests (PT, aPTT, platelet count) were normal for all four of these patients.

Using a cutoff of two or more positive answers, the sensitivity and specificity for the diagnosis of a bleeding

disorder were 89.5% and 98.6%, respectively (Table 3). A threshold of one or more positive answers increased sensitivity to 100% but decreased specificity (85.7%). A threshold of three or more positive answers decreased sensitivity to 42.1% but increased specificity to 100%. In a high-prevalence scenario (prevalence of bleeding disorders of 1%), a low HEMSTOP score (< 2) showed a low PPV (39.1%) but a very high NPV (99.9%), essentially ruling out bleeding disorders in patients from the general population with a normal score (a population that anesthesiologists typically encounter in their day-to-day practice). As platelet counts were normal in all patients *requiring precautions*, the addition of platelet count to routine coagulation tests did not add any value.

Discussion

Surgery and invasive procedures can be associated with excessive bleeding, which is influenced by both patient-related factors (e.g., constitutional hemostatic disorders, antithrombotic treatment, diseases that influence hemostasis) and the type of intervention. To assess the risk of perioperative bleeding prior to surgery or other invasive procedures, laboratory screening tests (usually PT, aPTT, and platelet count) are still widely used, although indiscriminate coagulation screening in unselected patients is not recommended.[5,6,29,30] Guidelines on preoperative assessment highlight the role of an accurate bleeding history, including details of personal and family history, previous post-traumatic or post-surgical hemorrhage and use of anti-thrombotic drugs. As no questionnaire on bleeding diathesis has been validated for the preoperative period, many anesthesiologists and other physicians still prescribe non-specific coagulation tests (PT, aPTT, platelet count) for reassurance. Nevertheless, a number of reviews[2,3] have shown both limited sensitivity and specificity of these tests. Given the low prevalence of bleeding disorders, ordering routine coagulation tests results on the one hand in a high number of false positives that leads to further unnecessary examinations, and on the other hand in numerous false negatives which lead to false reassurance. Similarly, standard hemostatic tests do not perform well in predicting the bleeding risk associated with regional anesthesia techniques, including neuraxial anesthesia. It is recommended that hemostasis testing should not be requested in patients whose history and clinical examination suggest no bleeding disorders, regardless of anesthesia type (general, neuraxial, peripheral, or combined).[7,31] In case of neuraxial anesthesia, intake of drugs that potentially interfere with hemostasis should be carefully considered, as acquired hemostatic disorder due to medication is one of the main risk factors for spinal/epidural hematoma.[32]

This study describes how a newly developed questionnaire was applied to a retrospective cohort of patients referred for a hemostatic evaluation because of their bleeding symptoms and to a prospective cohort of controls *a priori* unaffected by any hemostatic disorder. An appropriately trained healthcare provider can quickly complete the five general questions and the two questions specific to females contained in this questionnaire. Except for the female-specific items, some of the questions on the HEMSTOP score resemble those proposed by Rapaport.[11] While some of the items proposed by Rapaport are more subjective (e.g., "Have you ever bled for a long time? Was bleeding after surgery ever hard to stop?"), the HEMSTOP items focus on symptoms requiring a medical consultation or a specific treatment, thereby increasing the clinical relevance of bleeding events.

Patients diagnosed with a hemostatic disorder requiring bleeding prophylaxis or precautions had a higher median HEMSTOP score than patients not requiring such precautions. Controls, defined as people in good health and "never referred for hemostatic evaluation because of bleeding symptoms", had a median HEMSTOP score of zero. For the diagnosis of a bleeding disorder, a threshold of two or more positive answers resulted in good sensitivity (89.5%) and very good specificity (98.6%). Given the low prevalence of inherited bleeding disorders, PPV and NPV were 39.1% and 99.9%, respectively. The questionnaire performed much better than the systematic coagulation tests reported in many studies (sensitivity 0-33%; specificity 84-99%; PPV 0-29%; NPV 74-99%).[7] The present study showed that the sensitivity of PT and aPTT for detecting hemostatic abnormalities in patients *requiring precautions* was very poor (only 26.3%). It is not surprising that the standard coagulation tests were unhelpful, as the majority of bleeding disorders were vWDs or platelet disorders. The specificity of the PT and aPTT could not be evaluated in this study as they were not performed on the control subjects (theoretical specificity derived from normal distribution = 97.5%). The present questionnaire could accurately discriminate people without a disorder that increased the risk of bleeding (score < 2) from those with potential hemostatic disorders (score ≥ 2). It is estimated that about one patient in every 1,000 of the general population (NPV of 99.9%) might be a false negative—i.e., with HEMSTOP score < 2 but suffering from a bleeding disorder.

We suggest obtaining specialist advice in cases where the HEMSTOP score is ≥ 2, suggesting a bleeding disorder. As normal aPTT, PT, and platelet count results do not preclude the possibility of a hemostatic disorder or the risk of perioperative bleeding, specific laboratory assays should be performed depending on the bleeding symptoms and physical examination, family history,

medications/substances that potentially interfere with coagulation, and test availability. The hemostasis specialist should propose the precautions required in case of invasive procedures.

Our study has some limitations. First, as there are no referenced standards for the diagnosis of mild bleeding disorders, the study relied on diagnoses by experienced senior physicians working in an established hemostasis unit. It therefore cannot be excluded that, on occasion, symptomatic patients without a precisely diagnosed hemostatic disorder may in fact be affected by a rare constitutional bleeding disorder. For that reason, we chose a pragmatic approach. In the study design, we considered all patients for whom physicians had recommended treatment or precautions in case of surgery or an invasive procedure to be thusly affected (*requiring precautions).* Second, it is important to recognize that selection bias was an inevitable element of this study. Due to the retrospective design of the study and in order to have a historical diagnosis of an inherited bleeding disorder, the studied patients had initially presented with significant bleeding symptoms (mainly mucocutaneous symptoms or postoperative hemorrhages) which led to testing and a subsequent diagnosis. Therefore, it is not surprising to find positive scores in these patients. Moreover, patients referred for tests may have been more symptomatic (i.e., had more quantitative or qualitative bleeding events) than other patients suffering from mild bleeding disorders that could go undiagnosed. These biases may likely lead to an overestimation of the true HEMSTOP power of discrimination. Nevertheless, the HEMSTOP questionnaire was also able to discriminate between patients with an increased risk of bleeding and *requiring precautions* from those who were symptomatic but *not requiring precautions*. Another selection bias concerns the control population. Given the estimated prevalence of inherited bleeding disorder at close to 1%, it cannot be excluded that some controls might be affected by a hemostatic disorder. Nevertheless, it would not greatly alter the specificity, only in a conservative way. Furthermore, even within the limits of patient selection, we found that the sensitivity of the HEMSTOP questionnaire (89.5%) was far better than that of PT/aPTT testing (26.3%). Third, the questionnaire was not applied in the same manner to cases as to controls. Trained experts retrospectively administered the questionnaire for cases using the medical chart, while controls self-administered the questionnaire. Since it is important to be able to interpret bleeding symptoms, the questionnaire was designed to be completed by trained healthcare providers interviewing patients rather than by self-administration. As such, if a trained expert had administered the questionnaire, the control subjects may have answered the questions differently. In our view, however, the potential for bias impacting the results and diagnostic accuracy is unlikely as the HEMSTOP questions focused on symptoms requiring a medical consultation or a specific treatment.

In summary, we propose that a seven-item questionnaire, i.e., HEMSTOP, can be readily administered to patients prior to surgery or invasive procedures to help identify patients at increased risk for bleeding. We showed that the questionnaire discriminates patients at elevated risk for bleeding with recommended perioperative precautions from those without such recommendations as well as from healthy participants. Large prospective studies are required to assess and confirm the performance and usefulness of the questionnaire for preoperative evaluation.

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