Diagnostics and mechanisms of hemostasis

Impact paragraph

Patients with mild bleeding disorders suffer from disproportionate bleeding after minor injuries, surgery or delivery, leading to use of blood products, re-surgery or prolonged hospitalization[1,2]. In daily life, bleeding symptoms like epistaxis or heavy menstrual bleeding, can have a great impact on social and school or work-related activities and can lead to lower quality of life[3-6]. As pointed out in the preceding chapters, recognition and correct identification of mild bleeding disorders and establishing a personalized treatment plan, are crucial to prevent bleeding and its consequences, with accompanied economic and social benefits. However, in about 50-75% of the patients referred for bleeding evaluation, no reproducible abnormality in hemostatic laboratory tests is found[7-9]. In patients with bleeding of unknown cause (BUC), providing a personalized treatment plan ensuring save hemostasis for surgery or childbirth, and family counseling is difficult[10].

Patients with a hematologic malignancy often develop low platelet count due to their disease or its treatment. A prophylactic transfusion strategy does not prevent bleeding in all patients on the one hand, and is, on the other hand not always necessary[11,12]. A personalized transfusion strategy can prevent unwanted complications and can save costs[13].

The main goal of the studies described in this thesis is to improve diagnostic work-up in patients with a bleeding tendency, to determine the value and place of new diagnostic tests, and to gain more insight in the mechanism of bleeding in different patient populations. The results of this thesis are not only relevant for scientific purposes, but are also of importance in social and economic perspective. The knowledge gained in the preceding chapters of this thesis *(i)* enables critical appraisal and use of established diagnostic tests and diagnostic approaches and, *(ii)* reveals potential pathophysiological mechanisms of bleeding in patients with bleeding of unknown cause (PFA-only) and patients with chemotherapy induced thrombocytopenia (CIT).

Critical appraisal and use of established diagnostic tests and current diagnostic approaches in bleeding evaluation

The studies described in Chapter 2, 3 and 5 investigated widely used and accepted diagnostic tests and approaches in bleeding evaluation.

Chapter 2 revealed that the bleeding assessment tool (BAT) alone is of limited value in the diagnostic work-up of patients referred for bleeding evaluation. A negative BAT was not able to exclude a mild bleeding disorder and a positive BAT increased the likelihood of having a mild bleeding disorder. However, the value of this

increased likelihood in a referred setting is questionable. We believe that the main benefit of the BAT is that it provides a structured and complete interview of the patients' bleeding history. **Chapter 3** showed that both Multiplate and platelet function analyzer (PFA) were not suitable as screening tests for mild platelet function disorders in preoperative patients and patient referred to the hematologist for bleeding evaluation. Although the results of both studies might be regarded as 'negative' findings, and might not lead to significant changes in guidelines, they do have the potential to increase awareness of hematologists and other physicians treating patients with bleeding symptoms, leading to well considered use of the BAT, Multiplate and PFA.

In **Chapter 5** effectiveness, healthcare resource use and costs, and patient burden of two diagnostic approaches for patients referred for bleeding evaluation were compared. The newly proposed all-in-one diagnostic work-up was more effective and reduced patient burden, compared to the conventional stepwise approach, however this was at a higher cost. These findings open the discussion to what a conclusive diagnosis of a mild bleeding disorder and lower patient burden in the diagnostic process is worth. An important benefit of extensive bleeding evaluation, is the reassurance of complete investigation (even if no diagnosis is found) and the ability of putting together all the available pieces of evidence in order to carefully judge on the likelihood of having, or not having, a bleeding disorder.

Potential pathophysiological mechanisms of bleeding

In Chapter 4, 6 and 7, new experimental tests were evaluated in patients with bleeding of unknown cause (e.g. PFA-only patients) and patients with chemotherapy induced thrombocytopenia (CIT), in order to explore different mechanisms of bleeding. Our data adds new information to the recognized knowledge gaps of bleeding mechanisms in these patients. This will aid both physicians treating patients with congenital bleeding disorders and physicians treating patients with hematologic malignancies.

Chapter 4 described multiparameter microfluidic platelet function analysis in bleeding patients with a prolonged platelet function analyzer closure time as the only aberrant finding in their diagnostic work-up. Results showed altered microfluidic thrombus formation indicating a shear-dependent platelet function defect not detected by the static conventional hemostatic tests.

Chapter 6 described platelet activation processes and procoagulant activity in CIT patients and showed defective receptor signaling related to impaired mitochondrial function in platelets from these patients. In **Chapter 7** the fibrinolytic potential of whole blood clots of CIT patients was explored with tPA-ROTEM, before and after

platelet transfusion. Results showed that clots of CIT patients were more susceptible to tPA induced lysis compared to healthy individuals. Platelet transfusion resulted in less hyperfibrinolytic profiles, but not in all patients. Besides platelets, other factors are likely to influence clot lysis in CIT patients.

All studies are registered at the Dutch Trial Registry. Results described in this thesis have been, and will be, published in international peer review journals, and presented on (inter)national congresses. In this way, our results are shared with a broad audience of hematologists and other physicians treating bleeding patients and researchers in the field. We hope that in the end, we are able to change the statement 'we might never know why *most* patients bleed', into 'we might never know why *some* patients bleed'.

Reference

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