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Two situations give rise to development of point-of-care monitoring in the OR and ICU: i) the need to measure without delays the concentration or the biological effect of an anticoagulant (i.e. unfractionated heparin in cardiac bypass surgery, during angioplasty or haemodialysis); ii) some types of surgery are associated with a high amount of blood loss due to coagulopathy that requires a specific haemostatic replacement in a timely manner. The turnaround time of the entire process of conventional basic haemostasis testing in the central laboratory results in a risk of delay in diagnosis and consequently in appropriate treatment

Over many years POC coagulation-testing technology has improved considerably and it is now possible to perform a rapid, bedside coagulation test with just one drop (0,015 ml) or maximum 2 ml of whole blood. The test is generally carried out using a portable, hand-held, battery analyser. The analysis is performed on whole blood (instead of platelet-poor plasma as for analytical coagulation tests). One may assume that the substantial timesaving in obtaining coagulation results will improve blood product replacement therapy and conceivably improve patient outcome. Nevertheless, quality control has to be performed as for all procedures carried out in haemostasis laboratories. And last but not least, it is not evident to which speciality their cost has to be assigned.

MONITORS INVESTIGATING THE ANTICOAGULATION EFFECT OF HEPARINE**ACTIVATED CLOTTING TIME (ACT)**

ACT (Hemochron, International technidyne, INC) is the POC monitoring typically used in the OR, primarily in vascular and cardiac bypass surgery to evaluate effective anticoagulation with heparin. Blood loss and transfusion requirements in cardiac surgical patients may be reduced with more accurate control of heparin anticoagulation and its reversal with protamine [1].

HEMOCHRON Jr[®] microcirculation system performs different coagulation tests depending upon the cartridge chosen. The reproducibility of the activated coagulation time with celite (ACT-C) or kaolin (ACT-K) measured with the Hemochron[®] was calculated under different clinical conditions [2]. The ACT-C and ACT-K variation rate (V%) ranged between 5,6% and 10,8% and between 6,7% and 12,4% respectively. In clinical conditions of use, the authors observed that on-site haemostasis monitoring devices providing the most reproducible measurements are, in decreasing order, the thromboelastogram, the Hemochron, and the sonoclot. In heparinized patients and during CPB, results from different tests are not interchangeable, underlining the importance of established appropriate instrument-specific values for monitoring anticoagulation during cardiac surgery. It is well known that if aprotinin is given, kaolin should be used as the surface activator for ACT measurements under CPB surgery. Because CPB changes the sensitivity of ACT to heparin (haemodilution, hypothermia), some have advocated direct monitoring of heparin. The most common POC laboratory technique that measures whole blood heparin concentration is the protamine titration assay (Hepcon; Medtronic, Parker, CO).

VISCOELASTIC METHODS (POC COVERING THE ENTIRE FIELD OF HAEMOSTASIS FROM PLATELET FUNCTION TO FIBRINOLYSIS)**THE THROMBOELASTOGRAM (TEG)**

The thromboelastogram, which can be used as a near-patient device, analyses the visco-elastic properties of whole blood. It is currently used in cardiac and liver surgery, obstetrics, and intensive care as well as in trauma centres. In contrast to clotting tests, which by definition detect only a clotting time, TEG detects all phases of the coagulation process and fibrinolysis by measuring the change of elasticity during clotting and fibrinolysis. TEG detects the clot firmness i.e., the clot's mechanical stability. As the test is performed on whole blood, it detects the interaction of plasma factors, platelets and other cells, such as the participation of red cells in haemostasis. Accordingly, the thromboelastograph has proven itself as a useful tool in studies of clot lysis, of

red blood cell and platelet interactions, detection of the hypercoagulation state and the determination of clot structure and stiffness [3]. The R time is the time taken for the first fibrin strands to form, the Maximal Amplitude (MA) is the maximum strength of the clot. The alpha angle and k time reflect the kinetics of clot development. Finally, retraction of the clot occurs with eventual lysis, the Ly30 being a function of this [4]. TEG (Haemoscope Corporation, Morvon Grove, IL) has a relatively good predictive power for bleeding and TEG guided haemotherapy can lead to massive cost reductions, particularly by reducing the infusion of platelet concentrates, cryoprecipitate or fresh frozen plasma [5, 6, 7]. Moreover, in clinical conditions of use, the TEG provides the most reproducible measurements compared to other on-site haemostasis monitoring devices [3].

The ROTEM[®] (Modified Rotation Thromboelastogram analyzer)

Thromboelastography was generally performed without a direct activation step, so that reaction times were quite long. There was also very limited information available on the nature of an abnormal result, particularly in complex haemostatic disorders with activation and consumption in all relevant pathways of the coagulation process. Activated thromboelastogram (ROTEM[®], formerly ROTEG[®], rotation thromboelastogram analyzer, Pentapharm GMBH, Munich, Germany) is a new approach to coagulation assays. ROTEM[®] detects not only the abnormality of global haemostasis, but also can discriminate defective platelet function, fibrinogen polymerization disorders and deficiency, a lack in coagulation factors, heparin effects and hyperfibrinolysis as well as the beneficial effect of aprotinin therapy. The ROTEM[®] system uses a different power transduction system from conventional TEG devices, which makes it less susceptible to mechanical stress, movement, and vibration. ROTEM[®] tests are performed using an automatic pipetting system of citrated whole blood (300 mL). This provides a stable sample, allowing time to perform the test and requires minimum training. The following measurements may be performed: the INTEM monitors the coagulation intrinsic pathway (Factors XII, XI, IX, VIII, X, II, I, platelets) by activation of whole blood using a surface activator (partial thromboplastin from rabbit brain), the EXTEM monitors the extrinsic pathway (Factors VII, X, V, II, I, platelets) by activation of whole blood using tissue thromboplastin (rabbit brain extract), the HEPTTEM detects the heparin effect and is an INTEM analysis with heparin inactivation with heparinase, the APTEG confirms the presence of fibrinolysis as it analyses the EXTEM with in vitro inhibition of fibrinolytic activity through aprotinin. Compared with the EXTEM results, APTEG show evidence of hyperfibrinolytic activity after 5 minutes. Hyperfibrinolysis may lead to life-threatening bleeding and is probably an underestimated problem, as it has never been detected by clotting tests. Moreover, in a surgical setting, obstetrics or trauma, d-dimer assays are not helpful. The FIBTEM discriminates the contribution of platelets or fibrin to the clot by blocking platelets (EXTEM + GP IIb/IIIa antagonist). The NATEG is simply the recalcification of the citrated whole blood sample and gives a classical tracing of thromboelastography. The ROTEM[®] analysis relies on the continuous assessment of the clot firmness, allowing the determination of the onset of coagulation (CT, coagulation time-standard TEG: reaction time: r), kinetics of clot formation (CFT, clot formation time – standard coagulation TEG time: coagulation time k and maximum clot firmness (MCF- standard TEG: maximal amplitude: MA). Values for angle α and MA are higher than in conventional thromboelastography. The diagnostic information generated by the rotation thromboelastogram is more informative than a platelet count or typical clotting tests, such as APTT or PT values: stabilization of the clot and its premature dissolution are also investigated. This includes the platelet contribution to clot and factor XIII, which are not detected in clotting assays. However, a limitation of the thromboelastographic approach is its low sensitivity to defects in primary haemostasis, e.g., von Willebrand factor or aspirin intake, but nor are these situations detected by any classical coagulation tests or platelet count; they require different methods. The ROTEM[®] helps to restrict the use of blood products, to adjust the blood product replacement therapy or orient it towards antifibrinolytic agents. Modified computerized thromboelastography and platelet function analysis in routine cardiac surgery demonstrate high negative predictive values for postoperative bleeding, which supports treatment of surgical bleeding by distinguishing it from a significant coagulopathy [8]. Thromboelastography[®] is a better predictor for postoperative blood loss in cardiac surgery than PFA-100[®]. However, this new thromboelastography device deserves a new evaluation leading to a final validation, and hence to an international agreement [9].

SONOCLOT ANALYSIS

The coagulation process is detected by the resonance of the blood clot, which is dependant on its firmness (Hett). Although Sonoclot, analysed by an experienced observer, has shown to be predictive for clinical coagulation status during the perioperative period, it is less frequently used in comparison to TEG. The variation rate ranges between 5.8% and 33.6% according to different conditions and parameters and is the device that provides the least reproducible measurements compared to TEG, and ACT [3].

TABLE 1. VARIATION RATE OF DIFFERENT POC DEVICE

POC device	Variation rate
TEG (Haemoscope, # 3000)	3,1 – 9,5 %
SCT (Sienco Inc, # 401)	5,8 – 33,6 %
ACT-Celite (Hemochron, FTCA510)	5,6 – 10, 8 %
ACT-Kaolin (Hemochron, FTKACT)	6,7-12,4%

From [2]

POC TEST INVESTIGATING PLATELET FUNCTION.

PLATELET FUNCTION ANALYSER - PFA 100[®]

PFA-100[®] (Dade Behring) is a microprocessor-controlled device that provides an *in vitro* quantitative measure of primary, platelet-related haemostasis at high shear stress. The PFA-100 creates an artificial vessel consisting of a bioactive membrane reproducing the *in vivo* bleeding test. A controlled negative pressure aspirates anticoagulated blood (with sodium citrate) across a microscopic aperture cut into the membrane under steady high shear rates (5000-6000 sec⁻¹). The membrane is coated with equine type I 2 mcg collagen and either epinephrine bitartrate 10 mcg or adenosine-5'-diphosphate (ADP) 50 mcg. The presence of platelet antagonist and the high shear rates results in a platelet plug that gradually occludes the aperture. The time required to obtain full occlusion of the aperture is defined as the collagen/ADP closure time (CACT) or collagen/epinephrine closure time (CECT). Measurements of closure time by PFA-100 depend on functional platelets GPIIb and GPIIb/IIIa, von Willebrand factor, platelet count and haematocrit [10]. Currently, PFA-100[®] is reported to be superior to bleeding time as a screening test of primary haemostasis [11]. Some reports have found a significant correlation between PFA-100[®] results and platelet aggregometry [12]. Platelet dysfunction is recognized as an important reason for bleeding after cardiopulmonary bypass (CPB). Preliminary reports on the ability of PFA-100 to predict excessive blood loss associated with CPB gave disappointing results [13, 14]. In a recent study, measurements of closure time by PFA-100[®], performed after protamine-induced heparin neutralization, failed to predict bleeding after cardiac surgery [15]. Currently, PFA-100[®] proved useful after CPB to identify patients unlikely to benefit from platelets transfusion [16]. Haemodilution is common after cardiac surgery. PFA-100[®] will reliably detect platelet dysfunction only if the platelet count exceeds 100x10⁹ litre⁻¹ and the haematocrit is greater than 30%. These last two parameters are not taken into account for the standardization of the measurements of closure times. However, combined with the ROTEG[®] (now ROTEM[®], see TEG paragraph), the adenosine diphosphate-PFA test enhances the predictive accuracy of increased bleeding tendency after cardiopulmonary bypass [8]. Vincelot et al. evaluated platelet function in whole blood using the PFA-100[®] as part of the pre-anaesthetic coagulation testing screen during pregnancy. Although, no platelet aggregometry tests were performed to validate the results, the authors concluded that in patients with pregnancy-induced thrombocytopenia, platelet function assessed with PFA-100[®] may be preserved when the platelet count is as low as 60 x 10⁹ litre⁻¹ unless anaemia is present [17]. In women with pre-eclampsia, PFA-100[®] values remain near normal until the platelet count decreases to around 50 x 10⁹ litre⁻¹. However, the clinical value of PFA-100[®] in such patients remains to be demonstrated.

POC MONITORS INVESTIGATING PROTHROMBINE TIME, ACTIVATED PARTIAL THROMBOPLASTINE TIME.

COAGUCHEK-PLUS (BOEHRINGER, MANNHEIM, DIAGNOSTICS. FORMERLY, CIBA CORNING BIOTRACK 512)

Most current guidelines for blood-component therapy strongly recommend measurements of the prothrombine time (PT) and activated partial thromboplastine time (APTT) to guide transfusion of fresh frozen plasma (FFP) and cryoprecipitate [18]. Specifically, transfusion of FFP is beneficial to patients with

microvascular bleeding or haemorrhage who are massively transfused if the PT/APTT values exceed 1.5 times the laboratory's normal values. However, many of the decisions regarding transfusion of blood products are made on the basis of clinical judgment (> 1 blood volume loss), because of the delay (30 – 60 minutes) between sample draw and test completion. An immediately available and reliable result is critical for the patient. Coaguchek Pro DM[®] is a hand-held, portable coagulation monitor and performs instantaneous APTT, PT, INR. Disposable cartridges contain the reagents for PT, APTT. The PT reagent is rabbit brain thromboplastin (ISI 2) and the APTT reagents are bovine brain sulfatide as the activator and soybean phosphatide as the platelet substitute. Each cartridge contains an application well, a reagent chamber, and a reaction path. For each test, one drop of whole blood is applied in the appropriate cartridge. The blood is drawn by capillary action into a heated reagent chamber and continue along the reaction path until clot is formed. Clot formation is detected by a laser optical system, and the result is then standardized by a microprocessor to display the PT and APTT in seconds. This enables the calculation of INR by the microprocessor. APTT and PT testing requires no more than 150 sec from sample collection before results are available.

Several conflicting results have been published about the correlation between conventional tests and intraoperative monitoring of APTT and/or PT with the Coaguchek, most of them showing poor agreement with central lab results. One study in particular tested an algorithm to determine the need for coagulation factor transfusion [19]. Patients treated with on-site laboratory results (algorithm based therapy) received significantly fewer intraoperative FFP units (0.4 ± 1.1 U vs 2.4 ± 2.8 U) during treatment interval, had shorter operative durations and had decreased postoperative mediastinal chest tube drainage than did the patients in the standard-therapy group. They reported an acceptable accuracy for the Coaguchek-Plus monitor compared with laboratory standard assays [19]. In contrast, Nuttal et al. and Zalunardo found only moderate correlation with laboratory assays in cardiac surgery [20] or other surgical settings [21]. Coaguchek is probably more precise for PT and INR than for APTT [22]. It has also been used with great success for the self-adjustment of oral anticoagulant doses in selected patients [23].

It should be borne in mind, that the values provided by the portable monitor simply do not perform the analysis by the same process as the central lab, as the Coaguchek is performed on whole-blood and conventional APTT/PT is performed on platelet-poor plasma. Possibly, distinct cut-off values should be determined with the Coaguchek to guide transfusion therapy instead of assuming that the two techniques are interchangeable. However, bedside intraoperative monitoring of PT/APTT can provide valuable information for the patient's follow-up.

CONCLUSION

Quite a lot of haemostasis point-of-care monitors are now available in the operating theatre and have been developed to provide specific information of the haemostasis process. If these monitors are used correctly, the results seem to be reliable and some have been used to build algorithms for transfusion decision-making. However, their development requires close collaboration with haemostasis groups and quality control has to be established. Benefits to the patients need to be well documented to enable more widespread use of POC testing of haemostasis in different surgical settings. At least, studies of economic outcomes are required.

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