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Case Report

POINT-OF-CARE DIAGNOSTIC APPROACH IN A CRITICALLY ILL PATIENT WITH SEVERE BLEEDING FROM URINARY TRACT

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SUMMARY – Coagulation disorders in critically ill patients presenting with bleeding can be multicausal. The drugs applied can interfere and impair the coagulation cascade. Point-of-care (POC) coagulation assays may resolve difficult therapeutic situations in critical illness. We report on a 73-year-old critically ill male patient with massive hematuria after bladder lithotripsy. The patient was on low molecular weight heparin therapy due to recent pulmonary embolism. He was subjected to repeated surgical hemostasis which was ineffective despite massive transfusion protocol and normal standard coagulation profile. Additional POC coagulation assays were obtained and were indicative of platelet dysfunction. We revised his medical therapy and suspected the possible drug influence on platelet aggregation. After discontinuation of target drug, platelet aggregation increased whereas hematuria stopped. Coagulation disorders in intensive care unit patients are often multifactorial. Standard laboratory tests are unreliable in complex refractory bleeding and may result in inappropriate therapeutic decisions. Stepwise approach with assessment of clinical parameters, present therapy, and a combination of POC coagulation tests is the key to optimal therapeutic management.

Key words: *Amiodarone; Bleeding; Blood coagulation disorders; Blood coagulation tests; Drug-related side effects and adverse reactions; Platelet aggregation; Surgical hemostasis*

Introduction

Derangement of the coagulation system is a common phenomenon in critically ill patients, who may present with severe bleeding or/and a prothrombotic state[1,2]. The length of the surgical procedure and its invasiveness are factors that may be related to the intensity of bleeding. In addition to the surgical causes of coagulation disorders, the patient's inherited and acquired characteristics can significantly affect the coagulation process. While hypocoagulability and increased bleeding tendency may be observed in patients with hepatic dysfunction, phlebothrombosis will be more common in patients with tumors[3]. On the contrary, in patients suffering from inflammatory disorders, such as sepsis or urinary tract infections, both procoagulant and anticoagulant disorders are possible. Furthermore, systemic therapy may lead to changes in blood coagulation by acting on coagulation factor synthesis or by affecting platelet function. Therefore, drug interactions should always be kept in mind when a coagulation disorder occurs.

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There are many reasons for a disturbed coagulation cascade in the intensive care patients, and each of them may require specific therapeutic intervention[2]. Standard coagulation tests poorly reflect *in vivo* and real-time patient's coagulation profile, especially in critical illness. Additional point-of-care (POC) coagulation tests such as rotational thromboelastometry (ROTEM)[4] and tests of platelet function, which are based on aggregation[5], are introduced to clinical practice.

Case Report

We report on a 73-year-old male with a history of arterial hypertension and chronic atrial fibrillation, who presented with massive hematuria after therapeutic doses of low molecular weight heparin (LMWH) prescribed as therapy for acute pulmonary embolism as a complication after surgical lithotripsy of the urinary bladder. Because of worsening of atrial fibrillation, amiodarone was also introduced to therapy. He was admitted to the intensive care unit (ICU) with severe uncontrolled bleeding and hemodynamic instability. LMWH was immediately stopped and repeated surgical hemostasis with a massive transfusion protocol was done. His initial therapy was ciprofloxacin 800 mg/day, furosemide 40 mg/day, vasopressors, and inotropes in low doses (dobutamine and norepinephrine) with opioid analgosedation. Seven days after admission, there was clinical and laboratory presentation of active refractory bleeding from the urinary tract despite interventions. Repeated urine cultures were negative. He was repeatedly transfused with a total dose of 20 units of packed red blood cells,15 units of fresh frozen plasma, and cryoprecipitate, with several platelet pools according to standard laboratory tests. We also corrected ionized calcium concentration with established euthermia and normal pH values. Standard laboratory coagulation tests included prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen level, and platelet count. In the diagnostic setting of refractory bleeding and coagulation disorder, additional POC coagulation tests were performed, including viscoelastic hemostatic assay of rotational thromboelastometry (ROTEM) and platelet function tests (PFT), which included platelet aggregation with collagen (COL) and adenosine diphosphate (ADP). Multiplate analysis of PFT revealed platelet function disorders, with both COL and ADP. His medical therapy was revised and the possible influence of amiodarone on platelet aggregation/count was suspected. After stopping amiodarone and replacing it with an intravenous cardioselective beta-1 adrenergic antagonist (esmolol), repeated laboratory PFT showed increased platelet count and aggregation, whereas hematuria stopped within two days, as shown in Figure 1.

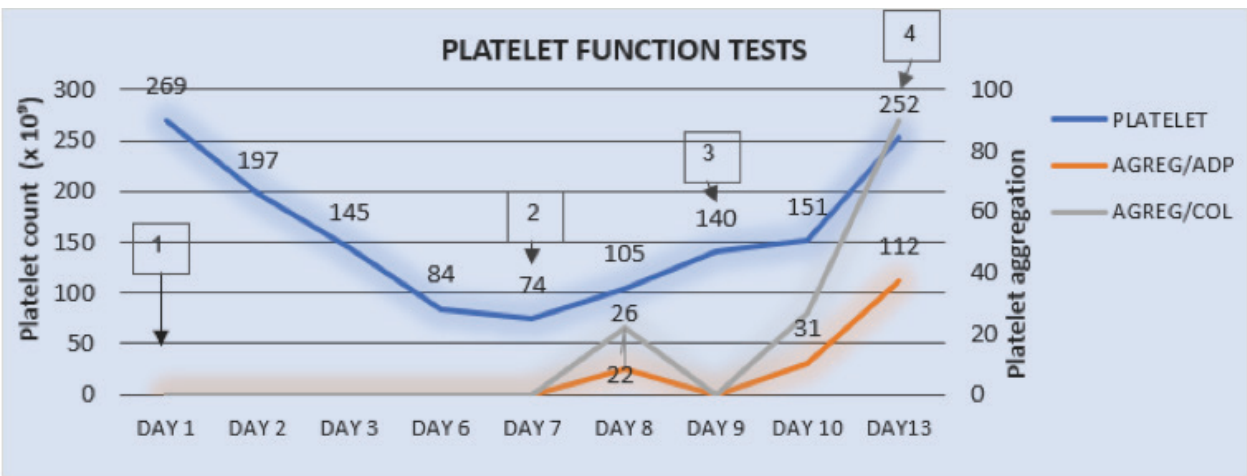

Fig. 1. Platelet function/count dynamics.

Clinical decision points (squares): 1) surgical hemostasis; 2) rebleeding, deficiency of coagulation factors (ROTEM), - FFP, platelet transfusion; 3) clinical suspicion of amiodarone-induced platelet dysfunction, discontinuation of therapy; 4) hemostasis, normalization of platelet function; AGREG = aggregation; ADP = adenosine diphosphate; COL = collagen.

Discussion

Coagulation disorders are common among critically ill patients and may range from simple coagulation defects to complex disorders[6]. An abnormal global clotting time (such as PT or APTT) occurs in 14%-28% of intensive care patients. The incidence of thrombocytopenia (platelet count $<150\times10^9$ L^{-1}) in critically ill medical patients is 35%-44%[1]. Critically ill patients have a four-fold to five-fold higher risk of developing hemorrhagic complications than patients with a normal coagulation status[2]. The most severe complication of anticoagulation therapy, especially in critical illness, is major bleeding[7]. Before anticoagulation begins, absolute contraindications need to be ruled out, including ongoing intracranial or another life-threatening bleeding, recent major surgical trauma, and thrombocytopenia $<30\times10^9$/L. Additionally, modifiable risk factors for bleeding should be identified and optimized. Multicausal variety of potential etiologies makes them challenging to manage in critical illness. Successful management of coagulation disorders requires prompt and accurate identification of the underlying cause, which can be challenging.

In the assessment of severe refractory bleeding, clinical presentation and additional coagulation tests targeting possible drug interference play a major role in appropriate diagnostic approach and optimal hemostatic therapy. Standard coagulation tests which are routinely performed include platelet count, global clotting assays, and measurement of coagulation factors. These might be misleading in clinically significant bleeding as they do not represent the complete coagulation cascade[7]. The most important coagulation defects that may remain undetected with routine coagulation tests are platelet dysfunction and hyper-fibrinolysis[8]. To overcome these limitations, especially in ICU patients, POC additional coagulation tests are introduced to clinical practice. Viscoelastic testing was first described by Hartert in 1948 and was established in the following years worldwide. Among them, ROTEM is widely used in Europe[9].

Different from standard coagulation assays, viscoelastic methods display clot formation and clot stability in real time. They permit detection of delayed initiation of coagulation, a reduced fibrinogen level, an increased fibrinolytic activity, and platelet contribution to whole blood coagulation. Viscoelastic tests are powerful tool in more complex bleeding scenarios such as trauma-induced coagulopathy, massive transfusion protocol, perioperative bleeding and targeted hemostatic therapy[9]. There are some course limitations to clinical applicability of viscoelastic testing, such as platelet inhibitors which can go unnoticed because of the high thrombin levels produced during viscoelastic testing. Platelets play a crucial role in hemostasis.

Management of critically ill patients is based on different multidrug therapy which can also interfere with the coagulation system making the coagulopathy even more challenging to resolve. Thrombocytopenia is commonly seen in laboratory findings in critically ill patients. Although the incidence is rare, drug-induced immune thrombocytopenia is a serious complication that is often overlooked as a cause of thrombocytopenia[10,11]. It has been reported that amiodarone is potentially able to induce thrombocytopenia[12,13]. In patients treated with amiodarone, serious toxic reactions have been described, including coagulation disorders with thrombocytopathy, even after administration of a single intravenous dose[14]. A variety of assay methods are available for quantitative assessment of the platelet function (PFT). Light transmission aggregometry is one of them and is considered as the gold standard test for platelet function evaluation. It measures the increase of light transmission through a cuvette of platelet-rich plasma when platelets aggregate upon the addition of stimulants such as adenosine diphosphate, collagen, epinephrine, arachidonic acid, or ristocetin[9]. The Multiplate® analyzer (Roche Diagnostics, EU) PFT allows platelet function to be assessed by using anticoagulated whole blood as a milieu without any sample processing. It measures the platelet ability to form aggregates in response to different agonists[15]. It is crucial to find the underlying cause of coagulopathy and to understand the limitations of various tests to assess them. Viscoelastic POC testing alone or combined with platelet function testing provides a prompt and more extensive diagnosis of coagulopathy and allows for targeted treatments in bleeding patients[7].

In our patient, coagulopathy was multifactorial and complex. He had several underlying causes of severe refractory bleeding. Therapeutic doses of LMWH resulted in postsurgical bleeding from the urinary tract. Critical illness with massive transfusion protocol and repeated surgical hemostasis can induce coagulopathy by itself. Although coagulopathy was not confirmed using standard laboratory tests, efficient hemostasis was not achieved. Additional POC tests were made, and platelet dysfunction was detected. Because of

multidrug therapy in ICU, we suspected the possible amiodarone drug interaction with platelet function. After excluding amiodarone from the patient's therapy, adequate hemostasis with platelet recovery was achieved.

Based on this case and review of current literature, we suggest a individualized and systematic approach to critically ill, bleeding patients in the ICU. With careful analysis of the patient's inherited and acquired coagulation disorders, current coagulation deficiency may be assumed, sequentially confirmed using appropriate coagulation tests, and successfully treated.

Conclusion

Coagulation disorders in critically ill patients are complex. Standard laboratory tests are unreliable in massive bleeding and may result in inappropriate therapeutic decisions. POC hemostatic assays such as ROTEM and PFT should be incorporated in coagulation assessment. A stepwise approach with assessment of clinical parameters, present therapy, and a combination of POC tests are crucial for optimal therapeutic management and achievement of adequate hemostasis.

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Sažetak

DIJAGNOSTIČKO-TERAPIJSKI PRISTUP KOMPLEKSNOJ KOAGULOPATIJI USLIJED RECIDIVIRAJUĆEG KRVARENJA IZ MOKRAĆNOG SUSTAVA

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Poremećaji koagulacije kod bolesnika u jedinici intenzivnog liječenja (JIL) su često složeni. Farmakoterapija tijekom bolesti može poremetiti fiziološki proces zgrušavanja krvi. Dodatni koagulacijski testovi uz standardni dijagnostički pristup kod nastale refraktorne koagulopatije omogućuju ciljano terapijsko djelovanje i postizanje hemostaze. Bolesnik u dobi od 73 godine u JIL se prezentirao masivnim krvarenjem iz mokraćnog mjehura nakon litotripsije i uvođenja terapijske doze niskomolekularnog heparina zbog akutne plućne embolije. Podvrgnut je višestrukim pokušajima kirurške hemostaze i masivnom transfuzijskom protokolu koji nisu doveli do prestanka krvarenja. Standardni koagulacijski testovi nisu ukazivali na poremećaj hemostaze. Dodatnim testovima utvrđena je disfunkcija cirkulirajućih trombocita. Nakon isključivanja lijekova koji mogu utjecati na njihovu funkciju došlo je do oporavka trombocitne funkcije i postizanja hemostaze. Koagulacijski poremećaji kod bolesnika u JIL-u su multifaktorski. Polipragmazija kod teško oboljelih može utjecati na fiziološki proces zgrušavanja krvi. Standardni koagulacijski testovi su nedovoljno pouzdani za razrješavanje kompleksnih koagulopatija. Sveobuhvatni klinički pristup, dodatni koagulacijski testovi i uzimanje u obzir utjecaja farmakoterapije na koagulacijsku kaskadu vodi do optimalnog terapijskog pristupa i postizanja hemostaze.

Ključne riječi: *Amiodaron; Krvarenje; Poremećaji koagulacije; Koagulacijski testovi; Agregacija trombocita; Kirurška hemostaza*