Massive bleeding - Section 1

Pathophysiology and general management of patients with massive blood loss

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Introduction

Massive blood loss (MBL) requiring massive blood transfusion (MBT) is common in critically ill patients (CIP) undergoing surgery for large trauma, organ transplantation, high-risk obstetrics, complex cardiovascular procedures and aggressive cancer.1-5 The hemostatic abnormalities of CIP have been discussed previously.6,7 MBT has been defined as: a) replacement of more than one blood volume (e.g., 10U of whole blood) in <24h; b) replacement of 50% of the total blood volume in 3h; c) transfusion of 20 units of packed red blood cells (PRBC). Early hypoperfusion or shock has been demonstrated to promote the hemostatic defects associated with MBL. For normal hemostasis is essential to correct hypothermia, acidosis and calcium levels. The role of hemostatic defects associated with MBT has been assessed since 1982.8 Early identification of hemostatic defects has been always considered essential to suggest transfusion therapy and to stop bleeding (Figure 1). MBT Protocols (MBTP) including fixed ratio PRBC/plasma/platelet concentrates for CIP have been proposed for many years since then to standardize treatment of MBL.9 In most centers there are predefined diagnosis and treatment protocols with rapid sequence timing of procedures, but this approach has never been standardized.

Pathophysiology and clinical settings

The hemostatic defects of MBL/MBT result from at least 3 mechanisms: 1) dilution or consumption of clotting factors with or without disseminated intravascular coagulation (DIC); 2) systemic fibrinolysis; 3) acquired platelet dysfunction.1-5 Dilutional coagulopathy is caused by replacement fluids lacking clotting factors or platelets (e.g., crystalloid and colloidal solutions or PRBC). An indirect relationship exists between the number of units of PRBC given and the decrease in clotting factors and platelets.8 When DIC complicates the clinical course of CIP, consumption of platelets and clotting factors is accelerated; platelet function can be inhibited by circulating fibrin degradation products assessed by D-dimer levels.10 MBL, particularly from the gastrointestinal tract, is common in CIP with advanced liver disease. CIP can develop systemic fibrinolysis with rapid lysis of thrombi at surgical sites and plasmin-induced destruction of circulating fibrinogen and other clotting factors.6,7 In addition to thrombocytopenia, platelet function can be impaired by high concentrations of fibrin or D-dimer, the premature release of platelet granular contents following intravascular platelet trauma (exhausted platelets). The time of PRBC storage must be always considered since PRBC start to have significant modifications after 5-7 days in relation to hyperkalemia and after 14-28 days regarding immune dysfunction, impaired vasoregulation and perfusion concerns. The thawing of frozen plasma (FFP) takes 15-30 min; therefore, its need should be anticipated when urgent transfusion is needed. One FFP unit increases the concentration of each of the clotting factors by 5%. Platelet concentrates (PC) are usually available immediately, although 10-15 min is required to pool the individual platelet packs: 10 U random donor platelet contain approximately 500 ml plasma (300 ml for a platelet apheresis product). In the absence of marked dilution or consumption, 8-10 bags of PC should raise the

Take Home Messages

- The hemostatic defects of massive bleeding result from at least 3 mechanisms: 1) dilution or consumption of clotting factors with or without disseminated intravascular coagulation (DIC); 2) systemic fibrinolysis; 3) acquired platelet dysfunction.1-5 Point-of-care (POC) such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) assays might be better than routine coagulation tests. However, frequent repetition of testing is necessary to recognize rapid changes of hemostasis in CIP with MBT.
- The use of POC such as TEG/ROTEM to assess the real-time hemostatic defects should be recommended but results should be centrally shared with hematologists who can suggest the appropriate blood components and hemostatic agents.
- Since each case might be different, a patient blood management approach is advised to delineate how blood components are ordered, prepared and delivered.
platelet count by 80,000/μL in the adult. A common cause of hyperfibrinolysis can be related to the administration of excessive volume of crystalloid contained in the cell salvage blood (hematocrit of 45-50%).

Diagnostic and clinical approaches to CIP with MBL/MBT
A practical approach to the hemostatic failure of CIP with MBL/MBT is to obtain laboratory tests both for diagnosis of hemostatic defects and as a guide to replacement therapy (Figure 2). An initial panel of routine tests must be always considered, followed by repeated testing at frequent intervals to monitor the impact of continued bleeding and sequential blood products replacement. Screening tests of hemostasis in CIP with dilutional coagulopathy show prolongation of the PT and APTT, reduced concentration of fibrinogen and thrombocytopenia.6,7

Very increased D-dimer might suggest DIC even though high D-dimer can be observed also in CIP with MBL: the DIC score as proposed by ISTH-SSC unfortunately is not always useful in MBL/MBT.8 Monitoring hemostasis is challenging because there is no validated test to assess the hemostatic impairment associated with MBL/MBT. Point-of-care (POC) such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) might be better than routine coagulation tests.11-13

Indeed, TEG/ROTEM assays offer a few advantages: 1) the turnaround time is shorter (15-30 min) then conventional assays, as these tests are done from whole blood, avoiding the need for sample centrifugation; 2) they can detect also hyperfibrinolysis of MBL not assessed by PT/PTT; 3) they may assess all the 3 phases of hemostasis such as primary platelet contribution, coagulation cascade and the role of factor XIII to cross-linking the fibrin clot, 4) TEG/ROTEM assays can be performed at room temperature. The use of TEG/ROTEM has been shown to reduce the transfusion requirements in MBL patients undergoing cardiovascular and liver transplantation surgery.11-13 However, frequent repetition of testing is necessary to recognize changes of hemostasis in CIP with MBL. Moreover, the assessment of conventional tests is sometimes useful to monitor the defects of hemostasis. Therefore, appropriate prospective clinical trials should be designed about the TEG/ROTEM-guided transfusion.

Current perspectives on massive bleeding

For optimal management of MBL/MBT effective and rapid organization is essential between hematologists at blood transfusion centers and clinicians at the patient's bed sites. The use of POC such as TEG/ROTEM to assess the real-time hemostatic defects should be recommended but their actual results should be centrally shared together with hematologists who can suggest the appropriate blood components and hemostatic agents. Moreover, the therapeutic approaches must be chosen according to the clinical settings such as obstetrical, surgical and traumatic events. FFP or fibrinogen were observed to be beneficial in MBL associated with obstetrical causes.16 Trauma patients treated with higher ratios of FFP and PC to PRBC could show better outcomes even though further clinical investigation is needed.1,5 Tranexamic acid (TA) has been shown to decrease mortality in trauma related MBL.17 The risk and benefits for other hemostatic therapies (prothrombin complex concentrates and recombinant activated factor VII) are not clearly defined in MBL/MBT.18,19 Based of the clinical data available the management of massive bleeding in CIP remains problematic. Since each case might be different, a patient blood management approach is advised to delineate how blood components are ordered, prepared and delivered; to determine lab test algorithms to use as transfusion paradigms; to outline duties and facilitate communication among involved personnel.

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