Editorial

Updates on Coagulation Management in Cardiac Surgery

Mahdi Najafi, MD[1*], David Faraoni, MD, FCCP[2]

[1]*Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran.*
[2]*Queen Fabiola Children's University Hospital (QFCUH), Free University of Brussels, Brussels, Belgium.*

Perioperative coagulopathy is regularly observed in patients undergoing cardiovascular surgery and is associated with massive bleeding, increased need for blood products transfusion, and re-exploration for surgical hemostasis. All these factors will exert a negative impact on postoperative morbidity, mortality, and costs.[1] Coagulopathy is related either to preoperative etiologies (e.g. anticoagulants, antiplatelet agents, and hereditary bleeding disorders) or to intraoperative factors (e.g. hemodilution, activation and consumption of coagulation factors and platelets, heparin administration, hypothermia, hypocalcaemia, metabolic acidosis, and excessive fibrinolysis).[2] Both preventive and therapeutic measures are recommended for the perioperative management of coagulopathy. A cornerstone of bleeding reduction and blood product administration is the prophylactic administration of antifibrinolytic agents. On the other hand, the increased availability of point-of-care (POC) devices for use in the perioperative setting has allowed rapid bedside assessment of coagulopathy. This new approach enables physicians to adopt a goal-directed approach in which therapy specifically targets the underlying hemostatic pathology.[3]

Preventive measures

The first step of this preventive approach is the preoperative assessment of coagulation status, treatments that interact with coagulation, and identification of the risk factors that could lead to intraoperative coagulopathy. Platelet dysfunction is a major source of bleeding during cardiovascular surgery, especially in patients treated with antiplatelet agents. Although platelet function assays are available, their role in evaluating actively bleeding patients has not yet been established. The 2011 Update of the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists' Blood Conservation Clinical Practice Guidelines recommended preoperative platelet function testing to determine the best timing of surgery in patients treated with Clopidogrel (ClassIIb recommendation, level of evidence C).[4] In a recent study, Mahla et al.[5] evaluated a strategy based on preoperative platelet function testing to determine the 'optimal' timing for coronary artery bypass graft surgery (CABG) in patients treated with Clopidogrel.[5] They observed that preoperative platelet function testing could be used to assess platelet function in Clopidogrel-treated patients and lead to a 50% shortened waiting period.

In the adult cardiac population, Karkouti et al.[6] reported that 22% to 30% of patients scheduled for a cardiac surgery with cardiopulmonary bypass (CPB) were anemic. Anemia in this population was associated with an increased risk of acute kidney injury and increased incidence of early and late mortality.[7] As a consequence, preoperative identification of anemia is now integrated into different multidisciplinary 'patient blood management' approaches.[8] Although there is growing evidence that preoperative hemoglobin optimization is feasible using iron supplementation, with or without the administration of recombinant human erythropoietin (rhEPO), further studies are needed to better define the efficacy and the safety of this approach.[9]

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[*]**Corresponding Author:** ***Mahdi Najafi,*** *Assistant Professor of Anesthesiology, Tehran University of Medical Sciences, Tehran Heart Center, North Karegar Street, Tehran, Iran. 1411713138. Telephone: +98 21 88029674. Fax: +98 21 88029724. E-mail: najafik@sina.tums.ac.ir.*

The other measure is the employment of autologous blood-saving methods. There are several methods for perioperative blood saving, including preoperative autologous blood donation, cell salvage, and retrograde autologous priming (RAP). Whereas preoperative autologous blood donation is no longer recommended, RAP is deemed vitally important[4] Indeed, RAP is readily possible to perform in most patients, while there are more limitations in the application of the other methods.[10]

Point of care

POC is the milestone of coagulopathy management in cardiac surgery. Standard laboratory tests for coagulation are performed using plasma and usually take 30-60 minutes to be reported.[11] In addition, standard laboratory tests only assess the initiation phase of clot formation and give no information on the amount of thrombin generated, the quality of the clot formed (amplitude), and the stability of the clot (fibrinolysis) (Figure 1). Conventional laboratory analyses in cardiac surgery include activated partial thromboplastin time (aPTT), International Normalization Ratio (INR), platelet count, and fibrinogen concentration. POC tests improve the quality of coagulopathy management, decrease costs, and reduce time to around 10 to 15 minutes.[12]

The activated clotting time (ACT) test is a standard coagulation assessment in cardiac surgery with CPB. This test has a high sensitivity but a very poor specificity.[13] Indeed, most anticoagulants (e.g. Aspirin, Clopidogrel) and factors such as low platelet count and dysfunction, and clotting factors deficiency didn't uniformly altered ACT. This leads to a high risk of inadequate management.[14]

Thromboelastography is a dynamic qualitative and quantitative evaluation of clot formation that consists of three stages: clot initiation, clot firmness, and clot stability (fibrinolysis).[15] Performing thromboelastography via the viscoelastic POC technique is feasible using two very similar devices, namely TEG® (Haemoscope Corporation, Niles, IL) and ROTEM® (TEMs International GmbH, Munich, Germany), both of which are increasingly employed in clinical practice. Although viscoelastic methods are very helpful, they do not obviate the need for other POC techniques that allow platelet function assessment (e.g.aggregometry).[16] Platelet function monitoring has been integrated into some algorithms. However, there is a paucity of evidence to support the routine use of these devices.[17] As much as POC techniques are potentially helpful in the diagnosis of coagulopathies, their role as predictors of coagulation disorders is more than controversial.[18]

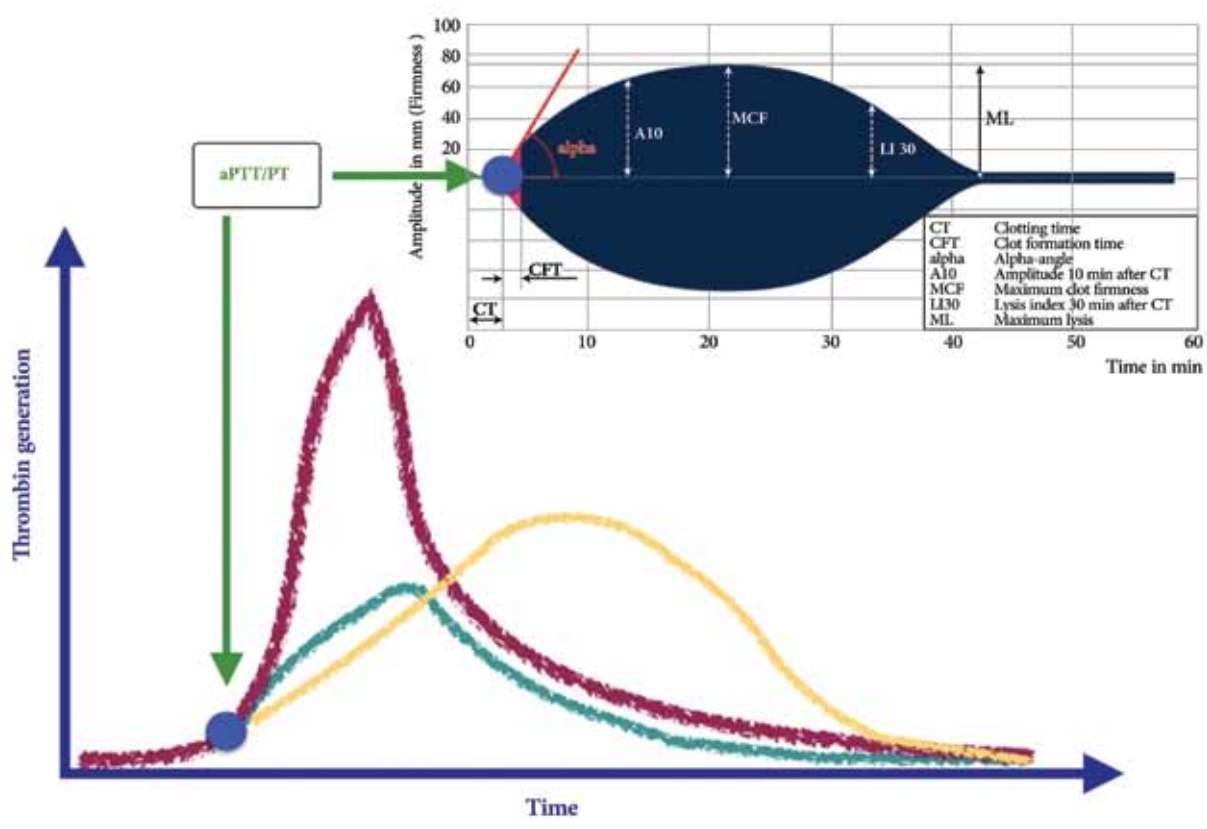

Figure 1. Schematic representation of aPTT/PT on normal and abnormal thrombin generation curves and on rotational thromboelastometry (ROTEM®)
aPTT, Activated partial thromboplastin time; PT, Prothrombin time

Therapeutic measures: the stepwise algorithm-based approach

The first step is to maintain or restore optimal physiologic conditions for hemostasis: body core temperature (> 36°C), blood pH (> 7.3), ionized serum calcium (> 4 mg/dL), and hematocrit concentration (> 25%).[19] Beside POC, the algorithm-based approach plays a pivotal role in the management of coagulopathy and hemostatic therapy.[19, 20] Confronting postoperative (post CPB) coagulopathy, we consider adequate Heparin antagonism, consistent clot stability/firmness by antifibrinolytics and blood products, and finally platelet dysfunction in a stepwise approach.[13, 21]

The plasmatic level of Heparin rather than the administered dose is appropriate for the determination of the 'optimal' protamine dosage. Studies show that usually excessive doses of protamine are administered in the clinical setting, which potentially increases coagulopathy and bleeding tendency.[22, 23]

Hyperfibrinolysis plays an important role in perioperative bleeding by causing clot instability and lysis. Antifibrinolytic agents are routinely administered to prevent excessive clot lysisby inhibiting the conversion of plasminogen to plasmin. Following the publication of the "Blood Conservation Using Antifibrinolytics: A Randomized Trial in a Cardiac Surgery Population (BART) study",[24] Aprotinin was removed from the market, although it is still available for compassionate use. However, Karkouti et al.[25] reported a retrospective single-center cohort study of 15365 cardiac surgical patients, 1017 of whom received Aprotinin and 14358 received Tranexamic acid (TXA).They noted that Aprotinin had a better risk-benefit profile than did TXA in high-risk, but not low- to moderate-risk, patients and suggested that its use in high-risk cases might therefore be warranted. In 2011, Health Canada concluded that the benefits of Aprotinin outweigh the risks when Aprotinin is used as authorized by Health Canada,[26] followed by the European Medicine's Agency in 2012.[27] The complete story has important lessons about clinical trials' designing and execution.[28]

TXA and Epsilon-aminocaproic acid (EACA) are the most routinely used antifibrinolytic agents in cardiac surgery. Recent meta-analyses have reported that the prophylactic administration of antifibrinolytic agents is associated with a decrease in perioperative bleeding and the need for blood transfusion.[29, 30] Although TXA is routinely used, the 'optimal' dosage is not yet known. As the administration of TXA could be associated with a dose-dependent increased incidence of seizures in patients undergoing open-heart surgery, further studies are needed to assess the relationship between lower dosages based on pharmacokinetics, blood loss, and the incidence of side effects.[30-32]

POC coagulation management with ROTEM® and impedance aggregometry is now frequently used to determine first-line therapy with specific coagulation factor concentrates such as fibrinogen concentrates and prothrombin complex concentrates (PCCs). In 2011, Gorlingeret al.[33] retrospectively reviewed more than 3000 patients managed before and after the implementation of an algorithm-based approach. The authors observed that the implementation of a coagulation management algorithm using POC devices significantly decreased blood product requirements as well as the incidence of thromboembolic complications. In 2012, Weber et al.[17] published the results of a prospective randomized trial in which they aimed to study the efficacy of hemostatic therapy guided either by conventional coagulation analyses or POC testing in coagulopathic cardiac surgery patients. Those patients in whom diffuse bleeding was diagnosed after Heparin reversal or increased blood loss during the first 24 postoperative hours were enrolled and randomized to the conventional group or the POC group. Hemostatic therapy algorithms in conjunction with POC testing reduced the number of transfused units of packed erythrocytes when compared with conventional laboratory coagulation testing. Moreover, POC-guided therapy was associated with decreased fresh frozen plasma (FFP) and platelet concentrates usage and costs as well as an improved clinical outcome.

In comparison with FFP, synthetic products are advantageous inasmuch as not only do they have lower volumes, possibility of rapid infusion, and risk of infection but also they obviate the need for cross-matching.[21] Nevertheless, physicians should keep in mind that the amount of FFP needed to obtain a significant increase in coagulation factors has been reported to be up to 30 ml/kg,[34] which could be associated with a high risk of transfusion-associated circulatory overload (TACO), acute respiratory distress syndrome (ARDS), and multiple organ dysfunctions (MODS).[35]

Fibrinogen plays a central role in the prevention and treatment of acquired bleeding in cardiac surgery. Fibrinogen is the first coagulation factor reaching critically low levels during major bleeding.[36] Cryoprecipitate is the main source of supplemental fibrinogen in North America. In Europe and Asia, fibrinogen concentrate has been approved for clinical usage.[37] Fibrinogen concentrate is a human product which is commercially available as a lyophilized powder. The dosage of fibrinogen in each 50 ml vial of concentrate is constantly around one gram (900-1300 mg) or 20 g/L; accordingly, it is very different from the amount of fibrinogen in each unit of FFP, which ranges from 1 to 3 g/L.[38]

On the one hand, it has been shown that low preoperative plasma levels of fibrinogen are associated with excessive bleeding after cardiac surgery.[39] On the other hand, the critical level of plasma fibrinogen that could trigger supplementation in bleeding patients has been challenging in recent years. First, the recommended threshold by the American Society of Anesthesiologists was 80 to 100 mg/dL[40] while it was recently changed to 150-200 mg/dL by the European Society

of Anesthesiology[41] and expert opinions.[37]

It is possible to individualize the dosage of fibrinogen concentrate to be administered based on the initial plasmatic fibrinogen level and the extent of bleeding. It is, however, important to know that the total required dose is usually much higher than 1-2 g, recommended as the initial dose.[37] Each vial of 1g fibrinogen concentrate increases the plasma fibrinogen level by 30 mg/dL.[42, 43] Thus, as it can be expected, the median dose of supplementary fibrinogen concentrate in bleeding cardiac patients ranges between 6 and 8 g.[37] This huge dose was recently used by Rahe-Meyer et al.,[44] who reported in a prospective trial that hemostatic therapy with fibrinogen concentrate in patients who underwent aortic surgery significantly reduced the transfusion of allogeneic blood products.

However, the use of factor concentrates as first-line therapies is still a matter of intense debate and further studies are urgently needed to define the behavior of fibrinogen levels during and after cardiac surgery, relationship between low fibrinogen levels and postoperative bleeding, adequate dose for fibrinogen supplementation, and efficacy and safety of fibrinogen concentrate supplementation.[45] A recent pilot study showed that giving fibrinogen in the initial stages of bleeding provided better coagulation state compared to supplemental platelet.[46] This study reconfirms the important role of fibrinogen in platelet aggregation.[37]

Prothrombin complex concentrate (PCC), which has been used principally to reverse Warfarin, depending on the product, contains factors II, VII, IX, and X as well as proteins C and S and Antithrombin and Heparin in various commercial brands.[13] PCC is probably an appropriate substitute for FFP after adequate supplementation of fibrinogen. Currently, there is no consensus on the dosage and timing for the administration of PCC, and the increased risk of thromboembolic complication should always be balanced for the administration of PCC.[13] With regard to single factors such asrecombinant factor VIIa (rFVIIa) and factor XIII, studies have shown that these factors have low efficacy in coagulation management.[47, 48] Since a recent meta-analysis reported that rFVIIa increases the risk of thromboembolic events,[49] rFVIIa should only be considered in cases of massive uncontrolled bleeding after the administration of routine hemostatic therapies.[48, 50]

Considering developments in equipment, medications, and diagnosis such as POC techniques, algorithms will undergo constant changes and guidelines will be revised extensively. Further investigations are still required to know about the optimum usage of POC devices, best algorithms for coagulation management, and best approach for the administration of coagulation factors.

References

1. Vivacqua A, Koch CG, Yousuf AM, Nowicki ER, Houghtaling PL, Blackstone EH, Sabik JF, 3rd.Morbidity of bleeding after cardiac surgery: is it blood transfusion, reoperation for bleeding, or both? Ann Thorac Surg 2011;91:1780-1790.
2. Ickx BE, Faraoni D. Management of the clotting system: a European perspective. Curr Opin Anaesthesiol 2012;25:80-85.
3. Spalding GJ, Hartrumpf M, Sierig T, Oesberg N, Kirschke CG, Albes JM. Cost reduction of perioperative coagulation management in cardiac surgery: value of «bedside» thromboelastography (ROTEM). Eur J CardiothoracSurg2007;31:1052-1057.
4. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, Saha SP, Song HK, Clough ER; Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion, Shore-Lesserson LJ, Goodnough LT, Mazer CD, Shander A, Stafford-Smith M, Waters J; International Consortium for Evidence Based Perfusion, Baker RA, Dickinson TA, FitzGerald DJ, Likosky DS, Shann KG. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011;1:944-982.
5. Mahla E, Suarez TA, Bliden KP, Rehak P, Metzler H, Sequeira AJ, Cho P, Sell J, Fan J, Antonino MJ, Tantry US, Gurbel PA. Platelet function measurement-based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing coronary artery bypass graft surgery: The timing based on platelet function strategy to reduce clopidogrel-associated bleeding related to CABG (TARGET-CABG) study. Circ Cardiovasc Interv 2012;5:261-269.
6. Karkouti K, Wijeysundra DN, Beattie WS. Risk associated with preoperative anemia in cardiac surgery: amulticenter cohort study. Circulation 2008;117:478-484.
7. Van Straten AH, Hamad MA, van Zundert AJ, Martens EJ, Schonberger JP, de Wolf AM. Preoperative hemoglobin level as a predictor of survival after coronary artery bypass grafting: a comparison with the matched general population. Circulation 2009;120:118-125.
8. Brevig J, McDonald J, Zelinka ES, Gallagher T, Jin R, Grunkemeier GL. Blood transfusion reduction in cardiac surgery: multidisciplinary approach at a community hospital. Ann Thorac Surg 2009;87:532-539.
9. Shander A, Van Aken H, Colomina MJ, Gombotz H, Hofmann A, Krauspe R, Lasocki S, Richards T, Slappendel R, Spahn DR. Patient blood management in Europe. Br J Anaesth 2012;109:55-68.
10. Vandewiele K, Bové T, De Somer FM, Dujardin D, Vanackere M, De Smet D, Moerman AT, Bouchez S, François K. The effect of retrograde autologous priming volume on haemodilution and transfusion requirements during cardiac surgery. Interact Cardio Vasc Thorac Surg 2013;16:778-783.
11. Toulon P, Ozier Y, Ankri A. Point-of-care versus central laboratory coagulation testing during haemorrhagic surgery. A multicenter study. Thromb Haemost 2009;101:394-401.
12. Haas T, Spielmann N, Mauch J. Comparison of thromboelastometry (ROTEM(R)) with standard plasmatic coagulation testing in paediatric surgery. Br J Anaesth 2012;108:36-41.
13. Faraoni D, Savan V, Levy JH, Theusinger OM. Goal-directed coagulation management in the perioperative period of cardiac surgery. J CardiothoracVascAnesth2013;27:1347-1354.
14. Baugh RF, Deemar KA, Zimmermann JJ. Heparinase in the activated clotting time assay: monitoring heparin-independent alterations in coagulation function. Anesth Analg 1992;74:201-205.
15. Ogawa S, Szlam F, Chen EP, Nishimura T, Kim H, Roback JD, Levy JH, Tanaka KA. A comparative evaluation of rotation thromboelastometry and standard coagulation tests in hemodilution-induced coagulation changes after cardiac surgery. Transfusion 2012;52:14-22.
16. Ferreiro JL, Sibbing D, Angiolillo DJ. Platelet function testing and risk of bleeding complications. ThrombHaemost2010;103:1128-1135.
17. Weber CF, Gorlinger K, Meininger D, Herrmann E, Bingold T, Moritz A, Cohn LH, Zacharowski K. Point-of-caretesting. A prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. Anesthesiology 2012;117:531-547.

18. Lee GC, Kicza AM, Liu KY, Nyman CB, Kaufman RM, Body SC. Does rotational thromboelastometry (ROTEM) improve prediction of bleeding after cardiac surgery? AnesthAnalg2012;115:499-506.
19. Avidan MS, Alcock EL, Da Fonseca J. Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery. Br J Anaesth 2004;92:178-186.
20. Steiner ME, Despotis GJ. Transfusion algorithms and how they apply to blood conservation: The high-risk cardiac surgical patient. Hematol Oncol Clin North Am 2007;21:177-184.
21. Weber CF, Klages M, Zacharowski K. Perioperative coagulation management during cardiac surgery. Curr Opin Anaesthesiol 2013;26:60-64.
22. Khan NU, Wayne CK, Barker J, Strang T. The effects of protamine overdose on coagulation parameters as measured by the thrombelasto- graph. Eur J Anaesthesiol2010;27:624-627.
23. Koster A, Borgermann J, Gummert J, Rudloff M, Zittermann A, Schirmer U. Protamine overdose and its impact on coagulation, bleeding, and transfusions after cardiopulmonary bypass: results of a randomized double-blind controlled pilot study. ClinApplThrombHemost2014;20:290-295.
24. Fergusson DA, Hebert PC, Mazer CD, Fremes S, Mac Adams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussières JS, Côté D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R; BART Investigators. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008;358:2319-2331.
25. Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, Tait G, Beattie WS. The risk-benefit profile of aprotinin versus tranexamic acid in cardiac surgery. AnesthAnalg 2010;110:21-29.
26. Health Canada. Final report-expert advisory panel on Trasylol (aprotinin) 2011. http://hc-sc.gc.ca/dhp-mps/medeff/advise-consult/eap-gce_trasylol/final_rep-rap-eng.php (3 February 2014)
27. European Medicines Agency. European Medicines Agency recommends lifting suspension of aprotinin: review finds that benefits of all antifibrinolytic medicines outweigh risks in restricted range of indications. http://www.ema.europa.eu/ema/pages/news_and_events/news/2012/02/news_detail_001447.jsp (3 February 2014).
28. McMullan V, Alston RP. Aprotinin and cardiac surgery: a sorry tale of evidence misused. Br J Anaesth 2013;110:675-678.
29. Meybohm P, Herrmann E, Nierhoff J, Zacharowski K. Aprotininmay increase mortality in low and intermediate risk but not in high risk cardiac surgical patients compared to tranexamic acid and ε-aminocaproic acid – a meta-analysis of randomised and observational trials of over 30.000 patients. PLo S ONE 2013;8:e58009.
30. Ortmann E, Besser MW, Klein AA. Antifibrinolytic agents in current anaesthetic practice. Br JAnaesth 2013;11:549-563.
31. Koster A, Bergermann J, Zittermann A, Lueth JU, Gillis-Januszewski T, Schirmer U. Moderate dosage of tranexamic acid during cardiac surgery with cardiopulmonary bypass and convulsive seizures: incidence and clinical outcome. Br J Anaesth 2013;110:34-40.
32. Faraoni D, Goobie SM. New insights about the use of tranexamic acid in children undergoing cardiac surgery: from pharmacokinetics to pharmacodynamics. Anesth Analg 2013;117:760-762.
33. Görlinger K, Dirkmann D, Hanke AA, Kamler M, Kottenberg E, Thielmann M, Jakob H, Peters J. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. Anesthesiology 2011;115:1179-1191.
34. Chowdhury P, Saayman AG, Paulus U, Findlay GP, Collins PW. Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. Br J Haematol 2004;125:69-73.
35. Benson A, Moss M, Silliman C. Transfusion-related acute lung injury (TRALI): a clinical review with emphasis on the critically ill. BJH 2009;174:431-443.
36. British Committee for Standards in Haematology, Stainsby D, MacLennan S, Thomas D, Isaac J, Hamilton PJ. Guidelines on the management of massive blood loss. Br J Haematol 2006;135:634-641.
37. Levy JH, Welsby I, Goodnough LT. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. Transfusion 2014;54:1389-1405.
38. Theusinger OM, Baulig W, Seifert B, Emmert MY, Spahn DR, Asmis LM.Relative concentrations of haemostatic factors and cytokines in solvent/detergent-treated and fresh-frozen plasma. Br J Anaesth 2011;106:505-511.
39. Waldén K, Jeppsson A, Nasic S, Backlund E, Karlsson M.Low preoperative fibrinogen plasma concentration is associated with excessive bleeding after cardiac operations. Ann Thorac Surg 2014;97:1199-1206.
40. American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology 2006;105:198-208.
41. Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CAA, De Robertis E, Filipescu DC, Fries D, Görlinger K, Haas T, Imberger G, Jacob M, Lancé M, Llau J, Mallett S, Meier J, Rahe-Meyer N, Samama CM, Smith A, Solomon C, Van der Linden P, Wikkelsø AJ, Wouters P, Wyffels P. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 2013;30:270-382.
42. Karlsson M, Ternstrom L, Hyllner M, Baghaei F, Flinck A, Skrtic S, Jeppsson A. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. Thromb Haemost 2009;102:137-144.
43. Solomon C, Schochl H, Hanke A, Calatzis A, Hagl C, Tanaka K, Rahe-Meyer N. Haemostatic therapy in coronary artery bypass graft patients with decreased platelet function: comparison of fibrinogen concentrate with allogeneic blood products. Scand J Clin Lab Invest 2012;72:121-128.
44. Rahe-Meyer N, Solomon C, Hanke A, Schmidt DS, Knoerzer D, Hochleitner G, Benny Sørensen B, Hagl C, Pichlmaier M. Effects of fibrinogen concentrateas first-line therapy during major aortic replacement surgery: arandomized, placebo-controlled trial. Anesthesiology 2013;118:40-50.
45. Ranucci M. Fibrinogen supplementation in cardiac surgery: Where are we now and where are we going? J CardiothoracVascAnesth2013;27:1-4.
46. Tanaka KA, Egan K, Szlam F, Ogawa S, Roback JD, Sreeram G, Guyton RA, Chen EP. Transfusion and hematologic variables after fibrinogen or platelet transfusion in valve replacement surgery: preliminary data of purified lyophilized human fibrinogen concentrate versus conventional transfusion. Transfusion 2014;54:109-118.
47. Karkouti K1, von Heymann C, Jespersen CM, Korte W, Levy JH, Ranucci M, Sellke FW, Song HK. Efficacy and safety of recombinant factor XIII on reducing blood transfusions in cardiac surgery: a randomized, placebo-controlled, multicenter clinical trial. J Thorac Cardiovasc Surg 2013;146:927-939.
48. Yank V, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, Sundaram V, McMahon D, Olkin I, McDonald KM, Owens DK, Stafford RS. Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. Ann Intern Med 2011;154:529-540.
49. Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med 2010;363:1791-1800.
50. Ponschab M, Landoni G, Biondi-Zoccai G, Bignami E, Frati E, Nicolotti D, Monaco F, Pappalardo F, Zangrillo A. Recombinant activated factor VII increases stroke in cardiac surgery: ameta-analysis. J Cardiothorac Vasc Anesth 2011;25:804-810.