Focused Update: European Society of Anesthesiology Guidelines on the Management of Severe Perioperative Bleeding

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European Society of Anesthesiology (ESA) guidelines on the management of severe perioperative bleeding (POB) were published recently. The scope and the process used for the preparation of the ESA guidelines were not strikingly different compared to previous guidelines on POB management: the ESA guidelines were written by European clinicians in an attempt to support colleagues' decision-making in the emergency situation of severe or massive POB. According to the methodology of the Cochrane Collaboration group, relevant clinical questions were defined to form the basis for the selection of search terms for the systematic literature review. Careful filtering resulted in the condensation of the identified body of evidence from over 20,000 to 1400 articles. Recommendations and suggestions were prepared according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. When grading the recommendations across outcomes, the GRADE system considers a certain degree of subjectivity, e.g. in the judgments of patient's values and preferences, balancing harms versus benefits, balancing benefits versus resource use and costs. Not surprisingly, the interpretation of the best-available evidence was performed from a European perspective, taking into account the heterogeneity in availability, licensing status, and costs of drugs and monitoring tests within this continent. The ESA guidelines underwent a review by external reviewers, the ESA Scientific Subcommittees, and the ESA members. Final approval was obtained from the ESA Guidelines Committee and the ESA Board.

Unlike guidelines from other societies and groups, the basis of clinical questions covered in the ESA guidelines is wide. In the ESA guidelines, POB management is not restricted to procoagulant strategies in overt POB but also includes patient optimization before, during and after bleeding. This holistic approach aims at increasing the patient's tolerance to bleeding-induced anemia that may evolve during the surgical procedure. Accordingly, chapters covering preoperative assessment and modification of bleeding risks, preoperative correction of preexisting anemia, optimization of the micro- and macrocirculation, and the basic interdisciplinary means of bleeding control are an integral part of the ESA guidelines. The respective ESA recommendations and suggestions can be summarized in a simple motto, “Be prepared and think ahead”. Furthermore, the ESA guidelines mirror the 3-pillar concept of...
patient blood management from the initial point within pillar 2: minimize blood loss and bleeding.

Another difference with previous guidelines is the emphasis on personalized medicine. According to the ESA guidelines, severe POB should not simply induce a reflex of ordering allogeneic blood products in a specific product ratio, e.g., one unit of plasma per unit of red blood cell concentrate. The restrictive use of labile allogeneic blood products is recommended in the guidelines because a liberal transfusion practice has been found to be associated with increased morbidity, mortality, and costs. Blood transfusions cannot reverse coagulopathy in severe POB. With the exception of life-threatening peripartum hemorrhage, an individualized therapeutic approach is recommended according to the concept of identifying the leading pathophysiological mechanisms of bleeding, followed by targeted and timely correction. The ESA guidelines include statements on the use of laboratory coagulation monitoring, including thromboelastometry (ROTEM) or thromboelastography (TEG) that may assist in the rapid detection of, for example, hyperfibrinolysis or fibrin deficit. In agreement with the Cochrane review on viscoelastic tests, the ESA guidelines conclude that guiding hemostatic interventions by ROTEM/TEG reduces bleeding. Moreover, algorithms incorporating predefined intervention triggers based on point-of-care assays are recommended according to the phrase, “Have a predefined plan”.

The European procoagulant treatment repertoire is discussed and graded in the ESA guidelines, including the pathophysiologically oriented use of, for example, antifibrinolytic drugs, desmopressin, and virus-inactivated coagulation factor concentrates. Here the saying is, “Give what is missing”. Recommendations and suggestions on the specific use of factor concentrates are in contrast to those of several other groups. For example, the ESA guidelines’ task force graded as “high” the evidence for the use of prothrombin complex concentrate (PCC) plus vitamin K in patients on oral anticoagulant therapy with POB, according to the results of prospective randomized clinical trials demonstrating improved patient outcomes (1B), while other groups discuss the preference for subcutaneous vitamin K. The use of fibrinogen concentrate is recommended in the ESA guidelines if significant bleeding is accompanied by low fibrinogen levels (< 1.5–2.0 g/dL) or low fibrinogen function according to ROTEM/TEG. Similarly, a recent Cochrane review concluded that fibrinogen concentrate, as the source of coagulation factor 1, appears to reduce transfusion requirements. Critique to this approach is partly driven by the misconception that coagulation factor concentrates would be an off-label recommendation. However, in several countries worldwide both inherited and acquired coagulation factor deficiencies are labeled indications.

The ESA guidelines provide evidence-based support in decision-making in various clinical settings, such as cardiovascular, orthopedic, pediatric, visceral, gynecological, obstetrical and neurosurgical procedures, as well as in bleeding patients with preexisting bleeding disorders or comorbidities associated with bleeding risks. In the accompanying editorial, the approach was acknowledged in the title, “All you ever wanted to know about perioperative bleeding”. Do we finally have all the answers required to permit prompt control of coagulopathic POB? I believe we don’t, because in many clinical fields the quality of evidence remains poor and much more research is warranted. Furthermore, any guideline is only useful in harmonizing and improving patient care and safety if applied appropriately in the clinical context. “The creation of guidelines, without significant attention to their adoption, is clearly a sterile exercise.” To support the availability of guideline contents at the bedside, the ESA launched a web-app summarizing the key messages. Publication in written form, smartphone tools, lectures at the
Euroanaesthesia meetings, clinical network trials, and e-learning material will most likely not suffice for the widespread adoption of the ESA guidelines. This will require user efforts to adapt the guidelines' recommendations to local requirements at the hospital level. For cross-sectional acceptance, the adoption process should ideally involve all medical disciplines and professional groups bearing responsibility for surgical patient care. An example for a national interdisciplinary and interprofessional consensus on the management of severe POB has recently been finalized. An example of a simplified hospital pocket guide for local use of procoagulant strategies is shown in Figure 1.

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**Checklist for the emergency management of severe or massive intraoperative bleeding at the Evangelical Hospital Vienna, Austria**

1. Avoid hypothermia < 34°C, pH < 7.2, hypocalcemia < 1 mmol/L.

2. Careful surgical technique, permissive hypotension, increase tolerance to anemia.

3. Risk for (local) hyperfibrinolysis (e.g., orthopedic surgery with tourniquet, severe trauma, shock): prophylaxis with tranexamic acid 10–20 mg/kg.

4. In case of overt severe bleeding (> 20% blood volume):
   a. If hyperfibrinolysis (according to ROTEM or reptilase time): tranexamic acid 15–20 mg/kg (before any procoagulant therapy).
   b. If fibrin deficit (FIBTEM A10 < 10 mm, fibrinogen concentration < 1.5 g/L): fibrinogen concentrate (dose calculation: approximately A10 increment x 0.55 or fibrinogen level increment x 4) (alternative: FFP > 30 mL/kg).
   c. If thrombin generation deficit (> 250% blood volume loss; EXTEM CT > 80s or indicative routine coagulation tests): prothrombin complex concentrate 20 U/kg (alternative: FFP > 30 mL/kg).
   d. If platelet deficit (according to ROTEM or platelet counts < 50 G/L): platelet concentrate.

5. Only as an ultimate measure after surgical and pharmacological interventions have failed and only after “preconditioning” with supplementation of substrates (fibrinogen, platelets) at pH > 7.2: recombinant factor VIIa (off-label use).

6. In case of overt severe bleeding in the presence of a normal ROTEM and/or history of antiplatelet drugs (+ indicative platelet function tests): desmopressin 0.3 µg/kg, if non-responsive to platelet concentrates.

7. In case of overt severe bleeding and history of vitamin K antagonists: reversal with prothrombin complex concentrate (dose calculation; 25–50 U/kg adjusted to actual INR).

8. In case of overt severe bleeding and history of direct oral antagonists: consider last intake, renal function, active charcoal, hemo(dia)filtration, reversal with prothrombin complex concentrate.

9. After heparin: consider reversal with protamine.

10. If factor XIII deficit (or indicative ROTEM): consider factor XIII concentrate.
The mission of the Network for Advancement of Transfusion Alternatives (NATA) can be understood as promoting a multidisciplinary approach to manage anemia, minimize blood loss, and optimize hemostasis, the use of blood products and the use of transfusion alternatives in order to improve patient outcomes14. The broad scope of the ESA guidelines strongly supports NATA's mission.

REFERENCES


