



Postoperative bleeding and coagulation disorders

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Purpose of review

New data have been made available in the field of haemostasis and thrombosis. Some long-awaited answers to important questions have been published, and some debates have benefited from an updated perspective.

Recent findings

Two important domains are addressed in this update: massive bleeding (1/1/1 ratios and fibrinogen concentrates) and the management of direct oral anticoagulants (monitoring and antidotes). Both are highly controversial topics. Higher plasma/platelets/red blood cells units ratios are now partly supported by a new study in trauma. Several studies show that preemptive doses of fibrinogen do not appear to bring any benefit. Monitoring of direct oral anticoagulants is now possible, and it has to be recommended in some circumstances. Specific antidotes are being developed, but there are still more questions than answers.

Summary

These new data should help anaesthesiologists and intensivists to better understand and manage massively bleeding patients or direct oral anticoagulants treated patients.

Keywords

antidotes, direct oral anticoagulants, fibrinogen concentrates, massive bleeding, transfusion

INTRODUCTION

Haemostasis and thrombosis are part of the daily landscape for anaesthesiologists and intensivists. The plenitude of literature in this field witnesses the importance of these topics for clinical practice. In 2015, some long-awaited answers to important questions have been published, and some lively debates have benefited from a new perspective. Two major topics have specially undergone very fast improvements: massive bleeding and the new direct oral anticoagulants (DOACs). We will focus on a few landmark studies and recommendations.

MASSIVE BLEEDING

The 1:1:1 ratio in severely bleeding patients

Since the early 2000s and the unfortunate Afghanistan and Iraq wars, many military (and several civilian) studies have focussed on the management of massive transfusion in severely bleeding trauma patients. For the first time, Borgman *et al.* [1] showed in 2007 that mortality decreased very significantly when higher ratios of fresh frozen plasma to red blood cells (RBC) were given to patients transfused with more than 10 RBC units in less than 24 h (widely accepted definition for massive transfusion).

Then, many retrospective series followed and confirmed these data. However, a major criticism always emerged about the importance of the survival bias: the more severe patients who died in the first hours had mechanically received less plasma than the surviving patients [2]. On the platelet transfusion side, Inaba *et al.* [3], from the same research group with John Holcomb, evidenced a comparable benefit of higher platelet units/RBC ratio on mortality. Further studies showed the same tendency. A retrospective study assessing the early (24 h) and late mortality (30 days) in severely bleeding trauma patients had shown that patients transfused with larger amounts of plasma and platelets had a much better outcome (survival) than patients with a more restricted plasma and platelet transfusion [4]. These data were confirmed by the

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KEY POINTS

- New evidence supports the use of higher plasma/platelets/red blood cells ratio in the massively transfused patients, but the optimal ratio is still unknown.
- Preemptive use of fibrinogen concentrates is not supported by recent RCTs.
- Monitoring of DOACs should be made available everywhere with the diluted thrombin time (Hemoclot) for dabigatran and the specific anti-Xa activity chromogenic assays for either rivaroxaban, apixaban and edoxaban.
- Specific antidotes are currently under development. Andexanet alpha (for Xa inhibitors) is especially promising. Idarucizumab (dabigatran) needs further data.

prospective PROMMTT study, but only for the first 24 h [5]. Therefore, it was likely that higher (and earlier) platelet and plasma amounts/ratios would benefit massively transfused trauma patients. A large and adequately powered randomized clinical trial (RCT) was needed, and the PROPPR study was performed [6]. Holcomb *et al.* randomized patients with severe trauma and major bleeding using plasma, platelets, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio. This was a pragmatic, phase III, multisite, randomized clinical trial of 680 severely injured patients who arrived in level I trauma centres. Early administration of a higher plasma, platelets, and red blood cells did not result in significant differences in mortality at 24 h or at 30 days (primary endpoint). However, more patients in the 1:1:1 group achieved haemostasis and fewer experienced death because of exsanguination by 24 h. Up to now, this is the only available study showing a beneficial trend of 1:1:1 ratios, even if a control group with common usual practice is lacking. Pending these positive results, it is highly unlikely that a study with a control group would be accepted on an ethical standpoint. The optimal ratio is still unknown.

Fibrinogen concentrates

A weak historical rationale based on the rapid decrease of fibrinogen concentration in the bleeding patient [7,8] and several uncontrolled studies have recently prompted the use of fibrinogen concentrates in emergency units and in operating theatres. This reminds about the pushy marketing process for recombinant activated factor VII supporters, and then came the negative data that did not confirm

what was expected. In addition, some point of care monitors companies (mainly viscoelastic tests) have advised to combine the observed decreased amplitude for TEG (maximum amplitude) or ROTEM (maximum clot firmness) in the bleeding patient with a supposed need for a supplementation with fibrinogen.

Two large randomized studies have been published in 2015–2016, and they obviously contradict some optimistic pilot studies and/or preliminary data. The Karlson group has just published the results of a prospective, randomized double-blind placebo-controlled study, performed in 48 low-risk, coronary artery by-pass graft (CABG) patients, and these results did not confirm the data from a pilot study which was much more favourable to fibrinogen [9,10]. Patients were randomized to infusion of 2 g fibrinogen or placebo immediately before surgery, after induction of anaesthesia. Median postoperative bleeding was not significantly different between the fibrinogen and placebo groups. The proportion of transfused patients, number of perioperative transfusions of allogeneic blood products and haemoglobin concentration 24 h after surgery were not significantly different between the fibrinogen and placebo groups, respectively.

In obstetrics, Wikkelsö *et al.* [11] have conducted an investigator-initiated, multicentre, double-blinded, parallel randomized controlled trial, including 249 patients with severe postpartum haemorrhage (PPH) who were assigned to a single dose of 2 g of fibrinogen concentrate or placebo (saline), independent of body weight and the fibrinogen concentration. At inclusion, the subjects had severe PPH, with a mean blood loss of 1459 (SD 476) ml and a mean fibrinogen concentration of 4.5 (SD 1.2) g/l. Postpartum blood transfusion was comparable in the fibrinogen group and in the placebo group. No thromboembolic events were detected. However, this study has some limitations: 46 patients could not be randomized in the trial because they were bleeding heavily and informed consent could not be obtained. These patients may have potentially benefited from the drug [12].

Only one study may be regarded as positive: Ranucci *et al.* [13] performed a randomized, double blind, placebo controlled trial in complex cardiac surgery patients. This single-centre study included 116 patients. In the fibrinogen concentrate group, the fibrinogen dose was calculated in order to reach a 22 mm ROTEM FIBTEM target 20 min before aortic cross-clamp removal (median fibrinogen dose 4 g). The total amount of RBC and FFP units transfused was significantly lower in the treatment arm. However, even if postoperative bleeding was significantly ($P=0.042$) less in the treatment arm (median,

300 ml; interquartile range, 200–400 ml) than in the control arm (median, 355 ml; interquartile range, 250–600 ml), the clinical relevance of such a difference is questionable. No safety issues were raised.

Actually, the administration of fibrinogen concentrates, either in bleeding patients (obstetrics) or preemptively (cardiac surgery) does not appear to be very effective, even if a significant decrease in red blood cell units requirements was observed in the Ranucci study. Further negative data are awaited, especially with the final publication of the REPLACE study in thoracic aortic surgery bleeding patients.

With regard to the never-ending debate comparing high plasma/platelet ratios with the so-called ‘theragnostic’ approach dealing with fibrinogen, prothrombin complex concentrates and viscoelastic guided algorithms, nothing can be concluded yet, as no large academic comparative study has been performed to favour one over the other.

DIRECT ORAL ANTICOAGULANTS

Monitoring

Biological monitoring has not been developed concomitantly with the first DOACs pivotal studies in atrial fibrillation-treated patients or in venous thromboembolism-treated patients, as it was generally assumed by the sponsors that these new treatments did not need any surveillance or monitoring. The rationale was very simple: well tolerated compounds, no monitoring, as compared with previous anticoagulant agents with cumbersome international normalized ratios (INRs) (vitamin K antagonists, VKAs) or anti-Xa (low molecular weight heparins) monitoring.

This is not that simple. These agents are indeed very promising, but they develop very potent anticoagulant activity. Therefore, from time to time, and in several settings (emergency, trauma, overdose, suicide, and so on), a biological dosing could be useful to help the physicians in managing these patients. Assessment of drug exposure may be needed. Fortunately, several dedicated tests are now available, the diluted thrombin time (Hemoclot) for dabigatran and the specific anti-Xa activity chromogenic assays for either rivaroxaban, apixaban and edoxaban. A reference document on the management of DOACs in nonvalvular atrial fibrillation patients has been issued by the European Society on Cardiology [14]. It could be entitled ‘What you always wanted to know about DOACs in the A-Fib patient’. Many recommendations are available and a full section is dedicated to biological monitoring. Especially for apixaban, rivaroxaban and edoxaban, these guidelines discourage the use

of either prothrombin time/INR or activated thromboplastin time (aPTT) in DOACs-treated patients. This had been already nicely shown by Gouin-Thibault *et al.* [15], who had demonstrated that patients with a high plasma concentration of apixaban (up to 400 ng/ml) could have a normal prothrombin time and aPTT. To put it in other words, measuring normal routine coagulation tests does not eliminate an overdose of apixaban in most of these patients.

Monitoring has to become now available everywhere, even if, as opposed to INR in VKA-treated patients, it will not be used to equilibrate the daily treatment, but to assess the exposure in some limited circumstances (Table 1).

Antidotes

As already stated, DOACs are now recognized as a major step forward for our patients. However, several issues may deserve our attention. Reports on the pharmacokinetics and pharmacodynamics for these agents show a major intra- and inter-individual variability and a high number of drug–drug interactions. In addition, alteration of renal function interferes with most of DOACs. As a result, an unexpected high number of major bleeding events have been reported, especially with dabigatran, focusing the attention on these new anticoagulant agents [16].

Prothrombin complex concentrates (PCC) and activated prothrombin complex concentrates (FEIBA) have been tested with various doses and conflicting results in different animal models [17,18] and healthy volunteers [19], and they are now used by clinicians in bleeding patients on a nonevidence-based basis, and with a variable efficacy. However, several series, especially in neurology/neurosurgery patients show a better outcome in patients treated with PCC [20].

Specific antidotes are also being developed. Three of them have already performed phase II and/or phase III studies:

- (1) Idarucizumab (Praxbind) is a fully humanized antibody fragment (Fab), which binds to the thrombin binding site of dabigatran, hence inactivating the molecule [21]. In healthy young and older volunteers, idarucizumab was associated with immediate, complete and sustained reversal of dabigatran-induced anticoagulation [22]. It was well tolerated with no unexpected or clinically relevant safety concerns. A phase III study is on-going (REVERSE-AD), including bleeding patients who have serious bleeding or require an urgent procedure. Preliminary results have been disclosed for

Table 1. Monitoring of direct oral anticoagulants (DOACs)

	Specific tests	Other tests, less accurate
Dabigatran	Diluted thrombin time (Haemoclot) Ecarin clotting time	Activated partial thromboplastin time (aPTT)
Rivaroxaban	Specific anti-Xa activity	Prothrombin time
Apixaban	Specific anti-Xa activity	None

the first 90 patients, showing a complete reversal of the anticoagulant effect of dabigatran within minutes and 20% mortality (mainly unrelated to the antibody) [23[■]]. Even if the European (EMA) and U.S. (FDA) regulators have granted an approval for this compound, we need further studies and a much larger number of patients to be fully reassured. Nevertheless, this antibody may save lives.

- (2) **Andexanet alpha** is a recombinant **modified human factor Xa protein** that **binds factor Xa inhibitors** [24]. This specific reversal agent is designed to **neutralize the anticoagulant effects** of both direct and indirect factor Xa inhibitors. Its **half-life is short** (less than **90 min**) and the **bolus** has to be combined with a continuous **IV infusion**. To date, no data are available after a 6 h administration. However, Andexanet appears to be very effective in healthy volunteers [25[■]] and the development plan is ongoing with phase III studies with apixaban-treated or rivaroxaban-treated patients. Yet no approval has been given (expected mid-2017), but the future of this agent appears very promising. At the same time, other similar agents are being developed by several research groups.
- (3) **PER977** is a small, synthetic, water-soluble, cationic molecule that is designed to **bind specifically to unfractionated heparin, low-molecular-weight heparin, to the new oral factor Xa inhibitors, and to the oral thrombin inhibitor, dabigatran** [26[■]]. Few data are available for the moment.

As DOACs are very effective and increasingly popular, more and more patients are shifting from VKA treatments to DOACs. As a result, the number of DOACs-treated patients undergoing an emergency procedure, a trauma or an overdose, is increasing steadily and the need for long lasting, well tolerated, user-friendly and cheap antidotes will increase.

CONCLUSION

No doubt that we still stand at the beginning of new complicated but exciting developments, either for severely bleeding patients or for the DOACs. While looking back a few years ago, we have to acknowledge that some ideas and concepts have already collapsed. Large, adequately powered RCTs have taught us that sometimes enthusiasm may be misleading, and that waiting for evidence is wiser.

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