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EDITORIAL I

Supplementation of fibrinogen in acquired bleeding disorders: experience, evidence, guidelines, and licences

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During major bleeding from surgery or after trauma, fibrinogen is the first coagulation factor to reach critical levels.[1 2] Fibrinogen is the precursor of fibrin, and adequate fibrinogen levels are a fundamental requirement for effective coagulation. Fibrinogen deficiency can be rapidly diagnosed with viscoelastic point-of-care tests (thromboelastometry and thrombelastography),[3] and after a positive diagnosis, fibrinogen supplementation is a priority in the management of bleeding.[2] Currently, there are three options for supplementing fibrinogen in acquired bleeding: cryoprecipitate, fresh-frozen plasma (FFP), and fibrinogen concentrate. Cryoprecipitate has been withdrawn from many European countries in response to significant safety concerns,[4] but it is still available in the USA and the UK. In general, cryoprecipitate is also no longer considered an appropriate therapy for the treatment of hereditary bleeding disorders due to the lack of anti-viral processing. Therefore, giving it to those with an acquired bleeding disorder is a double standard, although lifetime exposure is obviously less.[5] FFP is the first-line standard of care in many countries for replacement of coagulation factors during massive bleeding in clinical settings such as surgery and trauma. However, there is a need for blood group matching, thawing, and warming before administration and high transfusion volumes may be necessary, meaning that administration times are prolonged (>90 min in one study).[6] Allogeneic blood products are also associated with the risk of complications, including transfusion-related acute lung injury and pathogen transmission.[7 8] Importantly, the use of FFP has been associated with increased mortality, both compared with saline[9] and in patients developing acute lung injury.[7] Fibrinogen concentrate offers an attractive alternative to allogeneic blood products, as purification and viral inactivation during manufacture appear to minimize many of the risks associated with using blood products. It also allows rapid delivery of a standardized quantity of fibrinogen without causing haemodilution or volume overload.

Recently, the use of fibrinogen concentrate has come under criticism due to a lack of randomized clinical trials demonstrating its efficacy and safety.[10 11] FFP is the product most likely to be used instead of fibrinogen concentrate, but the evidence base for this product is poor. There are concerns regarding the design of most FFP studies, including small numbers of patients, and the potential for bias.[12] There is no consistent evidence to suggest that FFP confers significant survival benefit through either prophylactic or therapeutic use,[12] and a systematic review reported lack of support for the clinical effectiveness of FFP when considering a broad range of outcomes (FFP had a positive effect in 22% of trials but a negative effect in 28%).[13]

Although more prospective trials on fibrinogen concentrate are clearly needed, it has been licensed since 1963 (in Brazil, followed by other countries) and it is regarded as the standard of care for fibrinogen supplementation in countries such as Austria, Germany, and Switzerland. As reported in a recent systematic review, a growing body of clinical evidence describes consistently favourable outcomes when using fibrinogen concentrate perioperatively or in massive trauma.[13] A number of studies have found evidence

supporting the safety of fibrinogen concentrate with a low incidence of thrombotic events,[13 14] although studies in larger numbers of patients are needed. Efforts are on-going to improve the evidence base for fibrinogen concentrate. Nine prospective trials are underway in the settings of surgery, trauma, and post-partum haemorrhage (three phase II, three phase III, and three phase IV studies).[14] In comparison, seven trials are underway for FFP in acquired bleeding; the majority are observational studies, three aim to determine whether FFP administration can be reduced in various settings, and two are competitor trials with factor concentrates.[15]

Fibrinogen concentrate is recommended by some international guidelines (e.g. the European trauma guidelines)[16] for acquired bleeding. However, the licensed indications for fibrinogen concentrate differ between countries. To date, fibrinogen concentrate has broad approval in Austria, Brazil, Bulgaria, Germany, the Czech Republic, Hungary, Kuwait, the Netherlands, Portugal, Romania, Switzerland, Taiwan, and Turkey (essentially for use in any setting where fibrinogen supplementation is considered necessary). Recently, the Irish Blood Transfusion Service also replaced cryoprecipitate with fibrinogen concentrate without a formal licensing process.[17] However, in the UK and the USA, fibrinogen concentrate is only approved for congenital deficiency. In countries where fibrinogen concentrate is licensed for acquired bleeding, the evidence, guidelines, and licensing regulations may be considered as being aligned in advocating its use. However, in the UK and the USA, contradictions exist between evidence, guidelines, and licensing. For example, the British guidelines for the management of massive blood loss recommend transfusion of cryoprecipitate to supplement fibrinogen,[18] despite noting that cryoprecipitate exposes the patient to multiple donors. These guidelines mention that virus-inactivated fibrinogen concentrate is available in Europe, but not licensed in the UK. The British Committee for Standards in Haematology currently recommend using either fibrinogen concentrate or cryoprecipitate for correcting fibrinogen deficiency in patients with disseminated intravascular coagulation.[19] In addition, the British Advisory Committee on the Safety of Blood (SaBTO) recently discussed clinical preference for fibrinogen concentrate due to its favourable safety profile and the lack of robust clinical evidence for the effectiveness of cryoprecipitate (although a specific recommendation has not yet been made due to limited data).[20] These represent further examples where clinical evidence and guidelines may be at odds with local licensure.

Allogeneic blood products have been used for many decades and accepted into clinical practice. However, the rigorous clinical proof of safety and efficacy, as is required for the approval of new drugs today, has never been obtained. Given the high incidence and severity of adverse events associated with human blood transfusion, the current availability of potentially safer alternatives, and the lack of evidence demonstrating efficacy, it is unlikely that regulatory approval would be granted for their use today. In addition, allogeneic blood components would not necessarily be subject to regulatory requirements as rigorous as those required for licensing new therapeutic agents because they can be considered as body tissue or biologic. They may, therefore, be regarded differently from coagulation factor concentrates, which can more clearly be defined as drugs.

These points raise the fundamental question of what should guide clinical practice; international guidelines, national licensing of therapeutics, published clinical evidence, or daily clinical experience? Physicians are generally allowed to prescribe a medicine outside the terms of its licence, providing that the physician is convinced that the unlicensed therapy would better serve the patient's needs than an appropriately licensed alternative. In the treatment of acquired bleeding, a number of drugs are successfully used off-label. For example, recombinant activated factor VII (rFVIIa) is not licensed for acquired bleeding, and the Summary of Product Characteristics (point 4.8) has been recently changed and now clearly states that when rFVIIa is used outside the approved indications, there is a high risk of arterial thromboembolic adverse events, and concludes that safety and efficacy of rFVIIa have not been established outside the approved indications and therefore rFVIIa should not be used.[21] However, the efficacy of rFVIIa has been demonstrated in the setting of catastrophic, life-threatening bleeding, and its use has been described in many case series, randomized trials, and even international guidelines on blood conservation in cardiac surgery.[22] A recent randomized controlled trial confirmed the efficacy of rFVIIa in acquired bleeding after cardiac operations.[23] This study, however, as well as previous case series and case reports, highlighted that rFVIIa is associated with an increased risk of thromboembolic events.

In the USA, the FDA recognizes that the off-label use of approved drugs or medical devices may be important therapeutically, 'and may even constitute a medically recognised standard of care'.[24] Fibrinogen concentrate is already used off-label in a number of institutions,[25] and usage has increased over recent years,[26] including in countries where fibrinogen concentrate is not licensed for acquired bleeding.[26] It may be concluded that physicians are considering published evidence and guidelines as a more important influence than local licensure. However, because the treating physician is legally responsible for prescribing a drug off-label, there remains a risk that therapeutic decisions are unduly influenced by fear of litigation.

In conclusion, there are considerable differences between countries regarding how fibrinogen concentrate is used. It represents the standard of care for treatment of acquired bleeding in many, while in others, it is not indicated for such use and allogeneic blood products represent the standard of care. This raises the question as to whether the local licensing or internationally published evidence should drive the choice of treatment. As further evidence from high-quality prospective studies becomes available, we hope for improved future alignment between published evidence, treatment guidelines, and local licensure.

Declaration of interest

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