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EDITORIAL III

Fibrinogen concentrate: clinical reality and cautious Cochrane recommendation

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A recent systematic review, 'Fibrinogen concentrate in bleeding patients', published by The Cochrane Collaboration, aimed to assess the benefits and harms of fibrinogen concentrate compared with placebo or other treatments in bleeding patients.[1] We agree with the authors finding that fibrinogen concentrate reduces transfusion requirements for allogeneic blood products, as this is in line with previously published work.[2 3] In addition, the review did not identify any adverse events associated with fibrinogen concentrate; again, this is in line with previous findings.[4 5] However, we feel that the review also made a number of incorrect or misleading assertions which merit further discussion and clarification.

Firstly, the authors suggest that the use of fibrinogen concentrate should be confined 'to a controlled clinical setting or trial', a suggestion that has been made previously by Stanworth and Hunt.[6] However, if this principle were to be applied routinely, it would lead to the abolition of all blood bank products, including plasma and cryoprecipitate, until robust trial data became available.[7] This suggestion also ignores the fact that the most widely available fibrinogen concentrate has held a licence since 1963 in Brazil, since 1966 in Europe, has been licensed in its current pasteurized form since 1985, and is currently licensed for treatment of both congenital and acquired fibrinogen deficiencies in Argentina, Austria, Brazil, Bulgaria, the Czech Republic, Germany, Hungary, Iran, Kuwait, the Netherlands, Portugal, Romania, Switzerland, Taiwan, Tunisia, and Turkey.[8] Indeed, a number of recent guidelines recommend the use of fibrinogen concentrate in the bleeding patient, including the updated European trauma guidelines[9] and the European Society of Anaesthesiology guidelines;[10] both of these guidelines were published before the searches for the Cochrane analysis were completed. It should also be noted that fibrinogen concentrate has a licence for the treatment of congenital deficiencies in Australia, Canada, Israel, Mexico, New Zealand, Puerto Rico, the USA, and numerous EU countries. Any off-label use in these countries (e.g. in the setting of acquired bleeding) is at the discretion of the individual physician, taking into account the risk profile of the available alternative treatments.[11]

The authors of the Cochrane review also recommend not using fibrinogen concentrate in the clinical setting until further evidence is available. However, they give no suitable recommendation of an alternative treatment. This negligence could in fact endanger patients, as the alternatives for fibrinogen supplementation, that is, fresh-frozen plasma (FFP) and cryoprecipitate, are associated with a number of adverse events.[12] Furthermore, the efficacy and safety of cryoprecipitate have never been tested in the setting of a randomized controlled trial (RCT). A recent systematic review of FFP found no consistent evidence or significant benefit for its prophylactic or therapeutic use across a range of settings in which it is indicated;[13] FFP is also associated with increased morbidity.[14] Cryoprecipitate has been withdrawn from a number of European countries in response to safety concerns,[15] and in most countries in which it is still available, it is no longer used for hereditary bleeding disorders. In fact, as acknowledged in the Cochrane review, fibrinogen concentrate is now preferred to both cryoprecipitate and FFP in the hereditary setting, and so the continued use of these products for the treatment of acquired bleeding disorders represents a double standard.[16] In 2009, the Irish Blood Transfusion Service took the decision to withdraw cryoprecipitate and replace it with fibrinogen concentrate, despite a lack of formal licensing.[17] This decision was made to reduce the risk of pathogen transmission, and was supported by a lack of evidence suggesting any benefit of cryoprecipitate over fibrinogen concentrate.[17] In addition, the World Health Organization recently urged member states to 'promote the availability of transfusion alternatives'.[18] It is perhaps unethical for the Cochrane group to suggest that a newer treatment with a growing body of evidence should be shunned in favour of older treatments which, despite being in use since World War II, have never been proven or evaluated according to the Cochrane methodology and are associated with a number of safety concerns. Tradition should not factor in the decision-making process in clinical practice, and, in any case, one might argue that fibrinogen concentrate is rapidly becoming the 'traditional' (standard of care) treatment for acquired hypofibrinogenaemia in a number of countries, such as Austria, Germany, and Switzerland.[19]

A number of RCTs are currently taking place or are planned to investigate the use of fibrinogen concentrate in settings such as cardiac surgery and postpartum haemorrhage. Of course, the evidence gathered from such trials can and should be used to inform clinical practice in the future.[20] However, there are already numerous publications reporting the regular use of fibrinogen concentrate, particularly in centres across Europe.[17 21 22] There has also been a focus on the use of algorithms to guide individualized dosing of fibrinogen, often driven by point-of-care testing.[21 22] As fibrinogen is the first coagulation factor to decrease to critically low levels during haemorrhage,[23] the use of fibrinogen concentrate allows targeted replacement of a specific part of the coagulation cascade. Relying on blanket therapies such as plasma or cryoprecipitate, with all their associated risks, is taking a step backwards when we should be moving forward into an era of targeted, personalized medicine. Indeed, the Research Ethics Committee of the Canton Zurich recently refused permission for the centre to participate in the REPLACE trial (a prospective, randomized, placebo-controlled study investigating fibrinogen concentrate to control bleeding during cardiac surgery), as they considered it unethical to expose patients in the control arm to unnecessary FFP transfusions when patients outside the context of the study were receiving fibrinogen concentrate according to the institutional algorithm-based coagulation management guidelines, by which their exposure to blood products is reduced.

Another point that warrants clarification is the authors' description of infusion times. The authors suggest that mixing of fibrinogen concentrate takes 15 min; in fact, the manufacturer suggests this takes only 5–10 min. The authors also underestimate the amount of time it takes to prepare FFP and cryoprecipitate; these products take time to be ordered, tested for blood group compatibility (where necessary), and prepared for administration. Not every hospital has access to equipment to allow them to thaw frozen products in $<$15 min, as suggested by the authors of the review, and thawing takes 45 min at room temperature.[24] Taking all these factors into account, the entire blood product preparation process can take 60–90 min.[24 25] Pre-thawed or liquid (never frozen) plasmas can be used; however, these products are of limited availability, and are generally only accessible in a small number of large, tertiary care hospitals. The authors of this review are correct in their assertion that there is no recommended infusion rate for FFP; however, this is simply because there is a lack of clinical evidence from which an optimal infusion rate can be determined. The manufacturers of the

commercial plasma Octaplas recommend a rate of no more than 1 ml kg^{-1} min^{-1};[26] infusion at rates greater than this has been shown to result in citrate toxicity and hypocalcaemia.[26 27] Using the suggested rate, for a patient of 70 kg, and assuming a fibrinogen concentration for FFP of 2 g $litre^{-1}$,[28] it would take more than 35 min (and over 2 litre of FFP) to transfuse a 5 g fibrinogen dose. For fibrinogen concentrate, an optimal infusion rate of 5 ml min^{-1} is quoted by the manufacturers, as determined from the results of pharmacokinetics studies and RCTs. In a controlled setting, infusion of both fibrinogen concentrate and blood products should take place as slowly as possible; however, in an emergency situation, rapid infusion may be desirable. Studies in cardiovascular surgery have shown that it is possible to infuse 1 g fibrinogen concentrate in <20 s (i.e. 250 ml min^{-1}).[5 29]

Finally, despite the fact that none of the studies analysed in the Cochrane review addressed the cost–benefit issue, the authors of the Cochrane review chose to discuss the current cost of fibrinogen concentrate in one country, Denmark. However, the authors chose to quote the retail price of 657€, which includes both the margins added by the pharmacy and the VAT; it would be more appropriate to quote the pharmacy purchase price, which in Denmark is currently 479€.[30] The authors also failed to consider that costs will vary widely from region to region and are dependent upon a number of factors, such as the tax and healthcare systems of each individual country. Therefore, picking a price in just one European country to use as an example is of little benefit to the international readership of the Cochrane review. In addition, the authors neglected to discuss the equivalent costs of the alternatives, that is, FFP and cryoprecipitate. Without such a comparison, any stated costs are irrelevant and uninformative. In fact, determining the cost of allogeneics is a highly complex issue in need of detailed analysis, as the true cost of blood products is far higher than the direct acquisition cost of the product itself; indirect costs such as storage, preparation, thawing, processing, and compatability testing also have to be taken into account.[31] A previous discussion regarding the price of allogeneics in Sweden prompted the suggestion that health economics would benefit from the input of both clinicians and economists, as neither are in a position to fully understand all of the facts.[32]

In conclusion, we feel that the Cochrane review contains information that may mislead readers. Systematic reviews such as this should provide clear, unambiguous recommendations for clinicians to follow, and these recommendations should be clearly justified, particularly when they relate to a licensed product with a broad label that is now the standard of care in several countries. If alternative treatments are suggested, this should be in the knowledge that they are a safe and efficacious option for patients, rather than simply relying on 'tradition' and potentially outdated treatments that have themselves never been subjected to the appropriate research scrutiny.

Declaration of interest

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EDITORIAL IV

Surrogate measures, do they really describe anaesthetic state?

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Characterization of anaesthesia is tricky, in particular, to go beyond the usual definition of a 'state of non-responsiveness to various types of stimulations', and to find indicators useful for titrating drug administration. General anaesthesia is usually split into two main domains: unconsciousness (non-response to verbal stimulation and amnesia) and analgesia (non-response to noxious stimulations).[1 2] Unconsciousness may be directly assessed at induction of anaesthesia (loss of verbal contact) and after recovery (absence of recall), but usually not during maintenance. The adequacy of the balance between analgesia and stimulation can be clinically estimated through movement, haemodynamic changes, and autonomic nervous system responses (sweat and lacrimation, modification in pupil diameter); these clinical endpoints have limitations when used for titrating anaesthetic drugs in clinical practice, specifically in paralysed patients. Furthermore, as adequate anaesthesia is defined as non-responsiveness, clinical assessment cannot distinguish between adequate drug delivery and overdosing if overdosing does not induce adverse effects.