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LETTER TO THE EDITORS

Acquired factor XIII deficiency after desensitization as a potential contributor to postoperative bleeding: more than meets the eye

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Dear Sirs,

Recent studies highlight an increased incidence of major postoperative bleeding in ABO-incompatible living donor kidney transplant (ABOi-LDKT) recipients desensitized using apheresis systems. Investigators have reported incidences of 15–20% vs. 2–5% in ABO-compatible LDKT recipients [1–3].

Looking at the normal coagulation tests (INR and aPTT), most investigators exclude coagulopathies from loss of coagulation factors or anticoagulants used during plasmapheresis (PP) sessions. Some authors have reported that IVIg administration too close to surgery is associated with bleeding (50.0% vs. 4.5%) [4]. Anyway, with the exception of a single study reporting abnormally high aPTT due to excessive amount of heparin [5], moving from normal coagulation test results, most investigators have pointed to transient drops in platelet counts (due to extracorporeal centrifugation and circulation during PP) as the putative cause for increasing bleeding incidence. Actually, the platelet counts reported always remain in the safe range according to most surgical and transfusion medicine guidelines; so, investigating other pathogenetic mechanisms is advisable.

At least one hemorrhagic coagulopathy gets undetected by screening with INR and aPTT, namely factor XIII deficiency. Coagulation factor XIII is a 328 kDa heterotetramer with transglutaminase activity. Activated FXIII stabilizes fibrin clots at the end of the coagulation cascade by bridging fibrin molecules [6]. While genetically determined factor XIII deficiency is exceedingly rare (incidence 1 in 5000), acquired factor XIII deficiency can occur due to autoantibodies (inhibitors) [7], after treatment with tocilizumab [8], or after removal of large volumes of plasma. As factor XIII participates in neither intrinsic nor extrinsic pathways, that activity cannot be detected by routine coagulation tests. Irrespective of its cause, FXIII activity <10% is associated with bleeding even in nonsurgical patients. As most kidney transplant candidates have normal liver function tests, removed plasma is usually replaced with albumin rather than with fresh frozen plasma (FFP). Furthermore, factor XIII has a far longer half-life than other coagulation factors (9–10 days vs. <3 days). In summary, the ABOi-LDKT desensitization course invariably results in a major (exchanged volume-dependent) factor XIII loss (Focosi D, unpublished data) that can cause postoperative bleeding.

Hanafusa *et al.* [9,10] first reported that double filtration plasmapheresis (DFPP) profoundly decreases factor XIII. Although no method completely spares factor XIII, immunoabsorption plasmapheresis (IAPP) causes drops in factor XIII level by only 25–35% [11] and should be preferred if applicable. DFPP is the next preferred modality where IAPP is not suitable (e.g., for large patients, as IAPP column processes less plasma volume) but causes drops by 65–75% [11]. Simple PP is the most detrimental approach to factor XIII [4,12]: In such scenario, 100% replacement with FFP rather than albumin is highly recommended.

As postoperative bleeding leads to increased length of staying at hospital and increased morbidity and mortality, whenever full plasma replacement has not been performed with FFP, adding factor XIII dosing using quantitative assays [13] to the preoperative laboratory evaluations is definitively worth the money. Whenever deficiency is confirmed, replacement therapies can consist of FFP or cryoprecipitate, or, more specifically (but off-label), with factor XIII concentrates [14].

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Conflict of interest

I declare that I have no conflict of interest to disclose.

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