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INVITED COMMENTARY

How can we minimize bleeding complications in ABO-incompatible kidney transplant recipients?*

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*Invited commentary on "ABO-incompatible kidney transplant recipients have a higher bleeding risk after antigen-specific immunoadsorption" by de Weerd AE *et al.*

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The use of ABO-incompatible (ABOi) donor organs is a possible solution for the shortage of donor organs for transplantation; however, naturally occurring antibodies (Abs) against blood group A or B (A/B) carbohydrate determinants in sera are a major impediment to achieving successful transplantation. The use of plasmapheresis (PP) has been shown to be a necessary preconditioning component in ABOi kidney transplant. Removal of pathologic anti-A and anti-B Abs has been accomplished with a variety of apheresis modalities including plasma exchange (PE), fractional PE, and immunoadsorption (IA) techniques. Using these modalities in conjunction with potent modern immunosuppression, ABO-incompatible kidney transplants have achieved graft and patient survivals similar to that seen in ABO-compatible (ABOc) transplants.

de Weerd *et al.* in this issue [1] have performed a retrospective matched-cohort study to compare the incidence of intra-/postoperative bleeding complications in the two groups of patients submitted to ABOi kidney transplantation and to ABOc kidney transplantation. The preoperative desensitization regimen included PP, which was performed with a plasmafilter followed by IA of anti-ABO Abs, rituximab, tacrolimus, mycophenolate mofetil, prednisone, and immunoglobulins. In the cohort of 65 ABOi patients and 130 ABOc controls, they found that ABOi patients lost more blood intra-operatively than ABOc controls, received erythrocyte transfusions more than twice as frequently as the controls in the first 48 h postoperatively. From those findings, they conclude that antigen-specific IA prior to ABOi kidney transplantation exposes patients to a significantly higher bleeding risk than ABOc controls. The similar

finding has been recently demonstrated in the study analyzing U.S. Renal Data System registry data to study associations of ABOi live-donor kidney transplantation with clinical complications [2]. In this national cohort study, ABOi recipients experienced significantly higher incidence of infectious and hemorrhagic complications compared with ABOc recipients.

The mechanisms underlying the susceptibility to intra-/postoperative hemorrhagic complications in ABOi kidney transplantation recipients remain highly speculative.

One possible explanation would be that thrombocytopenia and/or platelet dysfunction, which may follow repeated PP as a consequence of the procedure and materials used, is associated with hemorrhagic diathesis in ABOi recipients. If this is the case, functional platelet components may need to be transfused to minimize bleeding complications. de Weerd *et al.* [1] showed that the number of IA-PP appeared to be strongly associated with the need for erythrocyte transfusion. As the unspecific binding of other coagulation factors during repeated IA possibly takes place, the replenishment of the corresponding factors may be also needed.

Instead of using absorptive columns that capture anti-A or anti-B Abs, double-filtration plasmapheresis (DFPP) is frequently used to remove Abs for preparing ABOi kidney transplantation. DFPP uses an albumin solution as supplementary fluid, which contains no coagulation factors. Hence, the procedure engenders a profound decrease in coagulation factors. The coagulation factor XIII (FXIII) produces bridges between fibrin molecules within the fibrin clot. The previous report described a profound decrease in FXIII levels during DFPP therapies to the degree where fatal bleeding can occur because the FXIII production rate is slow and, once removed, is only slightly recovered [3]. Its depletion cannot be detected by usual coagulation tests because the factor does not participate in either intrinsic or extrinsic coagulation pathways. From the viewpoint of FXIII, simple PE seems suitable for the last plasmapheresis before ABOi living related kidney transplantation [4]. This practice might be able to avoid bleeding complications during the perioperative period of ABOi kidney transplantation.

Kidney transplant recipients may have comorbidities requiring anticoagulation or antiplatelet therapy. It has been previously reported that a supratherapeutic activated partial thromboplastin times with perioperative heparin infusion is associated with the greatest risk of bleeding complication in those patients [5]. Anticoagulation has been also considered essential during PP. In the study by de Weerd *et al.* [1], unfractionated heparin infusion 1000 U/h was used to prevent clotting during PP. Instead of using unfractionated heparin, the use of nafamostat mesylate (NM) as an anticoagulant on circuit patency of PP might minimize bleeding complications during and/or after ABOi kidney transplantation. NM is a proteinase inhibitor and is known to exhibit an anticoagulant effect when it acts on the blood coagulators IX, X, XIIa, and VIIa [6]. NM has the physicochemical characteristic of being quickly metabolized in the liver and blood, thereby having a short half-life of 5–8 min. Further, because of its low molecular weight of 539.6 M, NM is easily removed from the body via extracorporeal circulation. Therefore, NM is used for preventing blood clot formation in the extracorporeal circulation in patients suffering from disseminative blood vessel coagulation, hemorrhagic lesion, or hemorrhagic tendency [7,8].

In the study by de Weerd *et al.*, all kidney transplant recipients received unfractionated heparin 12 000 IU/24 h from 4 h after renal artery anastomosis until postoperative day 5 as preemptive anticoagulation [1]. This might be also associated with increased risk of intra-/postoperative bleeding complications in their study. Taken together with a previous report demonstrated that preemptive anticoagulation was associated with a nonsignificant trend toward decreased allograft thrombosis [9], the use of preemptive anticoagulation should be considered cautiously in patients with high risk of bleeding complications.

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