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Heparin-coated dialyzer membranes: is non-inferiority good enough?

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Evidence on the optimal anticoagulation regimen for hemodialysis in patients at high bleeding risk is scarce. The HepZero study is the first large multinational study comparing two different anticoagulation strategies to avoid systemic heparinization. The use of a heparin-coated dialysis membrane proved to be non-inferior to saline infusion. Superiority of either treatment, however, could not be demonstrated. These findings challenge current guidelines but equally raise questions on the choice of either strategy as compared with regional citrate anticoagulation.

Kidney International (2014) **86**, 1084–1086. doi:10.1038/ki.2014.315

The development of clinical dialysis was closely intertwined with the development of an effective and relatively nontoxic anticoagulant that could be produced at low cost.¹ From the first-ever successful dialysis session on, heparin was the product of choice. To date, heparin and its low-molecular weight derivatives remain the mainstay anticoagulant for millions of hemodialysis treatments.² In the vast majority of dialysis facilities, dialysis prescription is inextricably linked to the prescription of (low-molecular weight) heparin and its use is questioned only in particular situations—for example, heparin-induced thrombocytopenia and high bleeding risk.

A multitude of alternative anticoagulation regimens have been developed, including argatroban, lepirudin, danaparoid, fondaparinux, prostacyclin, and nafamostat.^{2,3} Most of these equally lead to systemic anticoagulation, precluding their use in

patients at high bleeding risk. Options then include regional heparin anticoagulation (heparin infusion into the arterial line and protamine sulfate in the venous line), tight heparinization (using the minimally effective dose of heparin), regional citrate anticoagulation, or anticoagulation-free dialysis. Recently, acetate-free citrate-containing dialysate concentrates were introduced into clinical practice. Besides the advantages of acetate-free dialysate, this provides a modest local anticoagulant effect inside the dialyzer. Citrate-containing dialysate allows reduction of heparin dose while maintaining extracorporeal circuit patency and dialyzer clearances.⁴ Most national and international guidelines on hemodialysis and anticoagulation (Table 1) do not provide guidance or leave room for interpretation. Center practices vary, and the decision to use one or another is often made based on local experience rather than on evidence. Lack of evidence underlies this vacuum.

The HepZero study⁵ (this issue) is a rare example of a randomized controlled multinational trial on anticoagulation strategies for hemodialysis, conducted in ten centers across Europe and Canada. ‘Standard-of-care’ heparin-

free dialysis, defined by the authors as regular saline flushes or predilution hemodiafiltration, was compared against dialysis using a heparin-grafted membrane (Evodial, Gambro-Hospal). Two hundred fifty-one patients were randomly allocated to treatment with either a heparin-grafted membrane or the standard of care. Enrolled patients mostly (79.6%) displayed a high or very high bleeding risk score as classified according to Lohr and Schwab.⁶ The primary end point was successful completion of the first dialysis session according to well-defined criteria: absence of complete clotting of the dialyzer or venous air chamber; no change of dialyzer or blood lines; no additional interventions, including additional saline flushes to prevent clotting; and no early rinse-back leading to premature termination of the dialysis session. The primary end point was reached in 68.5% of patients randomized to the heparin-grafted membrane group as compared with 50.4% in standard of care. According to the prespecified statistical plan, use of a heparin-grafted membrane was non-inferior to saline infusion. Superiority, however, could not be demonstrated.

As high-quality evidence on the optimal choice of anticoagulation in patients at high risk of bleeding is limited (see Figure 1), the present HepZero study should be considered very timely. Results of the study align with a recent single-center study from France⁷ and clearly position the use of heparin-grafted membranes as a valid alternative to saline infusion (be it continuous or intermittent) in patients at high risk of bleeding.

An important question to be answered is whether the control group represents the best that can be achieved by standard of care. A *post hoc* analysis of the HepZero study showed a significant difference in success rate between centers using saline flushes (70.7%) and centers using predilution (48.4%, $P = 0.0005$).⁵ The study, however, does not provide a clear explanation for this noticeable difference. A recent single-center Australian study showed opposite findings, as patients

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Table 1 | Guidelines for anticoagulation in patients at high risk of bleeding

Association	Country or region	Year of publication	Guideline for anticoagulation in patients at high bleeding risk
National Kidney Foundation	United States	–	No specific guidelines
Kidney Disease: Improving Global Outcomes	Global	–	No specific guidelines
European Renal Best Practice	Europe	2002	In patients with increased bleeding risk, strategies that can induce systemic anticoagulation should be avoided. Treatment strategies that avoid this include: no use of anticoagulants with regular saline flushing, and regional citrate anticoagulation.
The Renal Association	United Kingdom	2009	The Association recommends that anticoagulation should be avoided or kept to a minimum in patients with a high risk of bleeding. This can be achieved by use of a high blood flow rate and regular flushing of the extracorporeal circuit with saline every 15–30 min or regional citrate infusion. (1C)
Nederlandse Federatie voor Nefrologie	The Netherlands	2013	Patients with high bleeding risk should be treated either by (1) predilution techniques using either saline bolus infusions or predilution hemodiafiltration, or (2) regional citrate anticoagulation according to local practice.
Nederlandstalige Belgische Vereniging voor Nefrologie/Groupement des Néphrologues Francophones de Belgique	Belgium	–	No specific national guidelines
Haute Autorité de Santé/Société de Néphrologie	France	–	No specific national guidelines
Deutsche Gesellschaft für Nephrologie	Germany	2006	The Dialysestandard does not mention specific guidelines for anticoagulation in patients with high risk of bleeding.
Società Italiana di Nefrologia	Italy	–	No specific national guidelines

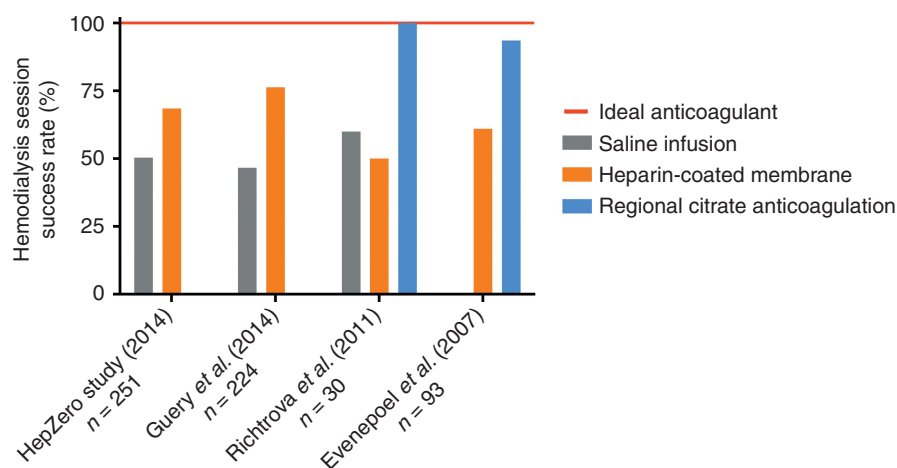


Figure 1 | Overview of recent trials comparing different systemic heparin-free dialysis regimens. The results of each study are expressed as the percent successful completion of prescribed dialysis sessions (*n* is the number of sessions taken into account for primary end point analysis), as reported from primary end point analysis of each study. In some of the original studies, detailed results of different strategies for saline infusion⁷ and regional citrate anticoagulation⁹ have been reported. For these studies the weighted average success rate for each strategy, that is, saline infusion versus regional citrate anticoagulation, has been given.

treated with continuous saline infusion were less likely to have clotted dialysis extracorporeal circuits (treatment completion 67 vs. 52%).⁸ Procedural differences, differences in the composition of membranes and tubings, and case mix may all account for these

discrepant findings. Nevertheless, the rates of clotting in the Australian study are comparable to those in the HepZero study, and there is no indication that either intermittent or continuous infusion of saline will ever result in a high degree of success.

But what about regional citrate anticoagulation? The authors of the HepZero study⁵ consider its application cumbersome. Delivering regional citrate anticoagulation requires additional pumps and close monitoring of plasma electrolytes, as it may lead to disturbances of the calcium and acid-base homeostasis. The most feared complication is severe hypocalcemia leading to cardiac arrhythmias. According to the authors of the HepZero study, fluid infusion is the gold standard of care in most centers. They suggest that regional citrate anticoagulation should be restricted to specialized dialysis centers. This may no longer hold true as more and more centers gain experience with citrate anticoagulation. Protocols to reduce complexity and risk of metabolic complications of regional citrate anticoagulation have been developed.⁹ Specialized centers even gain experience using citrate anticoagulation in patients with comorbidities previously considered as strict contraindications, such as cirrhosis.¹⁰ As this technique becomes more widely available, the most important question is whether it is superior as compared

with saline infusion and heparin-grafted membranes.

Few studies have addressed this question so far. We performed a prospective single-center study comparing two different strategies for regional citrate anticoagulation against use of heparin-coated membranes (Nephral 300ST, Gambro-Hospal) and clearly demonstrated superiority of regional citrate anticoagulation.⁹ Richtrova *et al.* recently confirmed that regional citrate anticoagulation is superior to both regular saline flushes and use of heparin-coated membranes.¹¹ These and other studies provide ample evidence in favor of regional citrate anticoagulation. What are lacking, however, are studies such as HepZero, multicenter multinational prospective studies that are adequately powered to unequivocally demonstrate whether regional citrate anticoagulation indeed is superior to other strategies.

Another issue needing clarification is the additional cost per treatment for patients at high bleeding risk. When accounting for the extra equipment, work load, and biochemical analyses, a previous study reported incremental costs of using a heparin-coated membrane and regional citrate anticoagulation, with the highest cost associated with the use of a heparin-coated membrane.⁹ The heparin-coated membrane used in the HepZero study (Evodial, Gambro-Hospal), however, requires less nursing time as compared with its predecessor. Cost of membranes and tubings, extra analyses, and nursing time should all be accounted in calculating the procedural costs. These costs differ substantially between dialysis centers.

Such calculations, however, do not take into account costs related to premature clotting, including direct

costs (consumables) and indirect costs (blood loss that may potentially require higher doses of erythropoiesis-stimulating agents or even blood transfusions). Moreover, patients confronted with repetitive clotting or premature termination of the dialysis session clearly perceive this as inadequate patient care. In some it may even lead to a significant loss of quality of life. The ultimate goal should thus be to strive for the perfect anticoagulant (Figure 1), that provides full anticoagulation of the extracorporeal circuit with minimal systemic effects and that comes at an affordable cost.

For the time being, insofar as guidelines address the choice of anticoagulant in high-bleeding-risk patients, the HepZero study⁵ warrants updating these documents. It is clear that in centers without the possibility for regional citrate anticoagulation, a heparin-coated membrane for now is a valid alternative to saline infusion in patients at high risk of bleeding. Nephrologists should, however, be aware that the risk of premature clotting of the extracorporeal circuit with either strategy remains as high as 30%. Regional citrate anticoagulation may prove more efficacious but is characterized by procedural complexity, hampering its widespread implementation.

As most dialysis centers are confronted with patients at high bleeding risk, the nephrological community should consider the HepZero study as a step in the direction of evidence-based systemic heparin-free dialysis. It is a prime example of how we should collect the necessary data, although it has not provided a definite answer.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

M. Ketteler (Germany), Z. Massy (France), A. Santoro (Italy), and B. De Moor (Belgium) are acknowledged for providing information on national guidelines.

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