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USE OF EVODIAL DIALIZERS FOR HEMODIALYSIS IN PATIENTS AT HIGH RISK FOR BLEEDING - SINGLE CENTRE EXPERIENCE

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Abstract

During hemodialysis the exposure of the blood to dialysis membrane can promote clotting, and hence, usually anticoagulation is used. In patients at increased risk for bleeding a heparin-free regime is mandatory. Evodial dialyzer contains a heparin-grafted membrane in order to reduce patients' bleeding risk. In this study we present our experience with the use of Evodial dialyzer.

We report on 106 dialysis sessions performed in 59 patients. Reasons for using Evodial: active bleeding, hematological conditions, complications of vascular access. Changes in the dialyzer or additional interventions were examined.

Low-dose unfractionated heparin was used in 10 (9.4%) sessions, and was added in 6 more and in another 5 saline flushes. In 4 sessions, due to coagulation we had to terminate dialysis.

Heparin-grafted dialyzers can be safely used in patients at high bleeding risk as a reasonable alternative when regional citrate anticoagulation is unavailable.

Keywords: Evodial, heparin-free dialysis, chronic kidney disease, high-risk for bleeding.

Introduction

In patients with end-stage renal disease (ESRD) hemodialysis (HD) is a life-preserving procedure. However, exposure of blood to extracorporeal circuit (ECC) activates blood cells and promotes inflammation cascade. Various dialysis membranes and tubing composition have been associated with various risks of clotting activation. Bio-incompatibility is also the major reason for adsorption of plasma proteins, platelet adhesion, and production of bradykinin (in white blood cells (WBCs) due to inflammation), blood clots, and thrombosis (1-3). Mainly high molecular weight proteins, such as albumin, fibrinogen, fibronectin, and globulins are adsorbed at the membrane surface. Platelet activation in the extracorporeal circuit accelerates thrombin generation via the intrinsic coagulation pathway. Occluding microthrombi (suspected clots in tubing or dialyzer membranes) and macrothrombi (visually evident clots in tubing or dialyzers) hinder dialysis efficiency, increase cost, and contribute to anemia via blood loss [4].

Hence, some form of anticoagulation is used to prevent this coagulation propensity within the circuit. The most efficient and studied anticoagulant is heparin, either unfractionated or fractionated (low molecular weight heparin - LMWH) [5,6].

However, the decision to administer anticoagulation begins with assessment of a patient's bleeding risk. Patients who are on HD are generally prothrombotic, especially after a surgical procedure, and have an increased risk of clotting in the dialysis circuit.

However, the risk of bleeding exceeds the risk of clotting in certain patient groups. These groups include patients with:

- severe thrombocytopenia (platelet count of <20,000/microL),

- evidence of active bleeding (from the gastrointestinal tract, intra-abdominal bleeding, extensive bleeding from surgical wounds, or from arterial or venous catheters at the time of dialysis),
- major surgery (especially intra-ocular and spinal surgeries) in the previous 72 hours,
- active intracranial or extradural hemorrhage,
- use of systemic anticoagulants,
- uremic pericarditis, coagulation factor VII or VIII deficiency.

These are so called patients at increased risk for bleeding and some form of heparin-free regimes is needed. In general, there are two types of heparin-free regimes.
The first is the use of non-heparin agents. Current options include direct thrombin inhibitors: argatroban [7,8] and hirudin [9,10], synthetic heparinoids (fondaparinux) [11,12], naturally occurring heparinoids (danaparoid) [13], and vitamin K antagonists (warfarin) [14].
Another well studied and utilized approach is the use of regional citrate anticoagulation (RCA). A single center in Slovenia reported performing over 10,000 successful dialysis sessions with RCA in 2015 [15].

The other regime is the use of anticoagulant-free hemodialysis. This can be achieved with either circuit priming or use of coated dialysis membrane.

The circuit priming method involves flushing the ECC with a solution that coats the plastic tubing, reducing interaction with the blood. The fluid is removed from the circuit prior to contact with the patient, minimizing systemic uptake. Studied priming techniques include saline, albumin, and citrate flushes, each with and without heparin ([16-20].

Another approach to anticoagulant-free HD is the use of coated dialyzer membranes. These membranes can be coated with heparin [21-24], albumin [25], and vitamin E1 [26,27) to reduce clotting. While this approach may reduce membrane surface clotting, it does little to achieve an anticoagulant effect in the remainder of the circuit.

Evodial dialyzer (Gambro-Hospal, Meyzieu, France) contains a heparin-grafted membrane (HGM) composed of a polyacrylonitrile sodium methallyl sulfonate copolymer; the manufacturing process includes a surface treatment with high-molecular-weight polyethyleneimine before heparin grafting. Parallel to the new hemodialyzer, Evodial blood lines were developed to improve characteristics of the extracorporeal circuit in terms of reduced activation of the coagulation system and lower deposits of clot components.

The aim is to provide a system (hemodialyzer and extracorporeal circuit) with a low thrombogenicity that can be used without or with low heparin dose in order to reduce patients' bleeding risk at the end of HD treatment. In vitro and in vivo data have shown the stability of heparin grafting with absolutely no release of heparin in the circulation. In a study conducted in 45 regular dialysis patients, Kessler *et al*. [28] found that the systemic heparin dose could be reduced by 45±13% without any coagulation issues.

An international, multicenter, randomized, controlled, open-label trial (HepZero study) [22] was designed to test the hypothesis that in patients at risk of bleeding NH-HD (non - heparin) treatment with HGM can be performed easily (without saline flushes or blood predilution) and is not inferior or even superior to the standard of care NH-HD treatment.

The primary end-point was reached in 68.5% of patients randomized to the heparin-grafted membrane group as compared to 50.4% in standard of care.

Aim

As high-quality evidence of the optimal choice of anticoagulation in patients at high risk of bleeding is limited, we wanted to show our experience with the use of Evodial dialyzer in high-risk patients.

Materials and methods

Patients

This single center retrospective study presents the results of 106 dialysis sessions in 59 patients performed with Evodial dialyzer in a period of 12 months.

These were the reasons for using Evodial: active bleeding, hematological conditions, complications of vascular access (Table 1).

Table 1. Rationale for using Evodial membrane

Conditions	Patients: total/percentage
Active bleeding	32 (54%)
Urogenital bleeding	11 (19%)
Gastrointestinal	13 (22%)
Respiratory	6 (10%)
Cerebrovascular	2 (3%)
Bleeding/complication of vascular access	27 (46%)
Systemic anticoagulant therapy	12 (20%)
Kidney biopsy	2 (2%)
Hematologic disease	16 (27%)

Double-needle vascular access was achieved through a native arteriovenous fistula (n=7) or a well-functioning double-lumen tunneled or non-tunneled central venous catheter (n=52).

Dialysis and anticoagulation

Each patient was dialyzed for 3 hours using B Brown machine Dialog+ with Evodial 1,3 and 1,6 dialyzer according to patient's BMI. Blood flow was set at 260 ml/min and dialysate flow at 500 ml/min in hemodialysis mode, and ultrafiltration rates were according to patient's interdialytic weight gain and clinical status.

After assessment of the risk for bleeding (see previously described conditions), dialysis was conducted without or with low-dose unfractionated heparin.

Results

Relevant demographic and clinical data of patients at baseline are summarized in Table 2. All flow settings were maintained according to the hospital dialysis protocol, low-dose UFH (1250 IE per session) was used in 10 sessions (from the start), and it was added in 6 more because of problems with coagulation. In 5 more saline flushing was added.

Four dialysis sessions were terminated earlier because of clotting. Table 3 shows the average dialysis duration and the ultrafiltration rates.

Table 2. Basic characteristics of patients

N=59	N mean + SD
Sex: m/f	30 /29
Age (years)	62.7 (+13)
Body weight (Kg)	74.9 (+11)
Laboratory findings	
Hb (g/L)	86 (+22)
Tr ($x10^9$/L)	205 (+132)
Albumin (g/L)	30.3(+7)
APTT (s)	50.4 (+30.9)
PT	26.7 (±29)

Table 3. Hemodialysis parameters

HD sessions N=106	N (%) / mean + SD
Arterial hypotension (%)	38
Duration of HD (mean + SD) (min)	200 (+24)
UF (l)	1 (+0.5)
Blood pump (ml/min)	257 (+35)
Blood clotting problems (%) Complete coagulation (%)	13 4
Use of anticoagulation during HD (%) from start added	16 10 6
Saline flush (%)	5

Discussion

Clotting in the extracorporeal hemodialysis circuit might result in premature termination of the treatment and, in worst case scenario, even blood loss corresponding to the extracorporeal circuit volume.

Although this is most often avoided by a liberal use of anticoagulant agents, several patient's conditions (active bleeding or increased risk of bleeding) might necessitate use of reduced or even zero systemic anticoagulation. There is little evidence for the best protocol for heparin free regimes.

They include saline flush, online predilution, regional citrate or use of heparin-grafted membrane.

The present observational study investigated the safety of using Evodial dialyzer in patients at high risk for bleeding. Although the reasons for using Evodial dialyzers were various (active bleeding, complications of vascular access, or hematological disease) the end results were satisfactory.

In only four sessions, the dialysis had to be prematurely terminated due to clotting. In majority of our patients, we performed dialysis without using heparin; only in 10 sessions we used low-dose UFH from the beginning of the session, and in 6 more we had to add heparin and in 5 saline flush due to risk of clotting.

These results were similar to those reported by Kessler [28] and in the HepZero study [22].

The use of heparin-coated Evodial dialyzer, manufactured with polyethyleneimine on the blood-side surface to reduce electronegativity and resulting in capacity to adsorb heparin could be considered a worthy alternative in cases where bleeding might be a problem. This should result in less or no clotting even in cases of no systemic anticoagulation.

Although results are worse than the those reported in the literature where regional citrate anticoagulation is used, it can be reasonable alternative when RCA is unavailable.

Conclusion

While the majority of hemodialysis sessions are performed with some form of anticoagulation (unfractionated or LMWH), there is a group of patients at high bleeding risk where use of anticoagulation is contraindicated. Heparin-grafted dialyzers can be safely used in patients at high risk for bleeding.

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