Effects of differences in dialyzers and anti-coagulant dosage on blood activation

Naoaki Taguchi [*1], Isao Tsukamoto [*2], Yoshihisa Yamashita [*2], Ayako Yamashita [*1], Noriyuki Fukaya [*1], Yuima Okamura [*1], Souichi Sugahara [*3], and Hiromichi Suzuki [*3]

[*1] Okamura Memorial Clinic, 230-1, Kuritsubo, Hidaka-shi, Saitama 350-1245, Japan, [*2] Division of Blood Purification, and [*3] Department of Nephrology, Saitama Medical University Saitama, Japan

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*1 Okamura Memorial Clinic, 230-1, Kuritsubo, Hidaka-shi, Saitama 350-1245, Japan, *2 Division of Blood Purification, and *3 Department of Nephrology, Saitama Medical University, Saitama, Japan

Introduction

Polysulfone (PS) is gaining recognition from the perspective of biocompatibility, as a dialysis membrane material that causes minimal activation of blood coagulation. However, even the same membrane material may influence blood coagulation differently, for example when assessed by residual blood in the dialyzer after dialysis [1]. As also cited in a report by the Statistical Research Committee of the Japanese Society for Dialysis Therapy, cerebrovascular and cardiovascular complications are often the cause of death for dialysis patients [2]. Prolonged improvement in the quality of dialysis, as a result of minimizing its impact on blood and blood vessels, is needed more than even before. Therefore, a dialyzer that succeeds in suppressing blood coagulation should help, over the long term, when performing dialysis and may also help in limiting the risk of cardiovascular complications including vascular problems [3].

As reported here, the current work studied the effects of differences in the residual blood in the dialyzer after a dialysis session to assess the anti-coagulation property of a minimum heparin dosage for individual dialyzers. Moreover, lipid metabolism during dialysis was also evaluated.

Subjects and Methods

The subjects were 7 maintenance dialysis patients (5 male, 2 female) with an age of 53.4 ± 14.7 years. The underlying disorder in these patients was diabetic nephropathy in 5 cases and chronic glomerulonephritis in 2 cases. Their time on dialysis was 8.0 ± 2.5 years, and their dry weight was 59.9 ± 14.4 kg.

The dialyzers used were REXEED-15A† (REXEED-A, Asahi Kasei Medical, PS), FDY-150GW (FDY-GW, Nikkiso, polyester-polymer alloy), and TS-1.6UL (TS-UL, Toray Medical, PS). The study period was 3 months; the subjects were crossed over to a different dialyzer each month, and the minimum required heparin dosage was determined as follows. The extent of residual blood was assessed on a 3-level scale (level I: virtually no fibers thrombosed, level II: small amount, thrombi are noted in small groups of hollow fibers, and level III: thrombi are noted in approximately half of the hollow fibers overall) [4]. Heparin was administered continuously starting at 10 U/kg/h and increasing/decreasing in steps of 100U/h depending on the residual blood assessment after a dialysis session following blood return. A bolus injection of heparin was not administered in this study. Accordingly, the minimum required dosage of heparin was defined as the dosage that, at the level I endpoint, caused a change from level I to level II. Free-fatty acid (FFA), triglyceride (TG), lipoprotein lipase (LPL), and activated partial thromboplasti time (APTT) were measured for each dialyzer at the minimum required heparin dosage as factors for the assessment of blood activation. FFA and TG were measured at 7 points: prior to the start of dialysis, 15 min, 30 min, 1 hour, 2 hours, and 3 hours after the start of dialysis, and at the completion of dialysis. LPL was measured at 5 points: prior to the start of dialysis, 15 min, 30 min, and 1 hour after the start of dialysis, and at the completion of dialysis. APTT was measured hourly after the start of dialysis. All measurements are indicated as mean ± standard deviation (SD). Statistical processing was done using a Wilcoxon rank sum test (Wilcoxon t-test), with $P < 0.05$ indicating a significant difference.

† The Japanese trade name of REXEED-15A is APS-15SA.

Results

1. Minimum required heparin dosage

The minimum required heparin dosage for each dialyzer was 5.5 ± 3.0, 12.6 ± 3.0, and 9.5 ± 1.9 U/kg/h for REXEED-A, TS-UL, and FDY-GW, respectively. The dosage was significantly lower for REXEED-A than for TS-UL and FDY-GW (Fig. 1). With regard to changes in the APTT, REXEED-A, which had the lowest required heparin dosage, also showed the lowest elevation of APTT from the beginning of dialysis until its completion (Fig. 2).

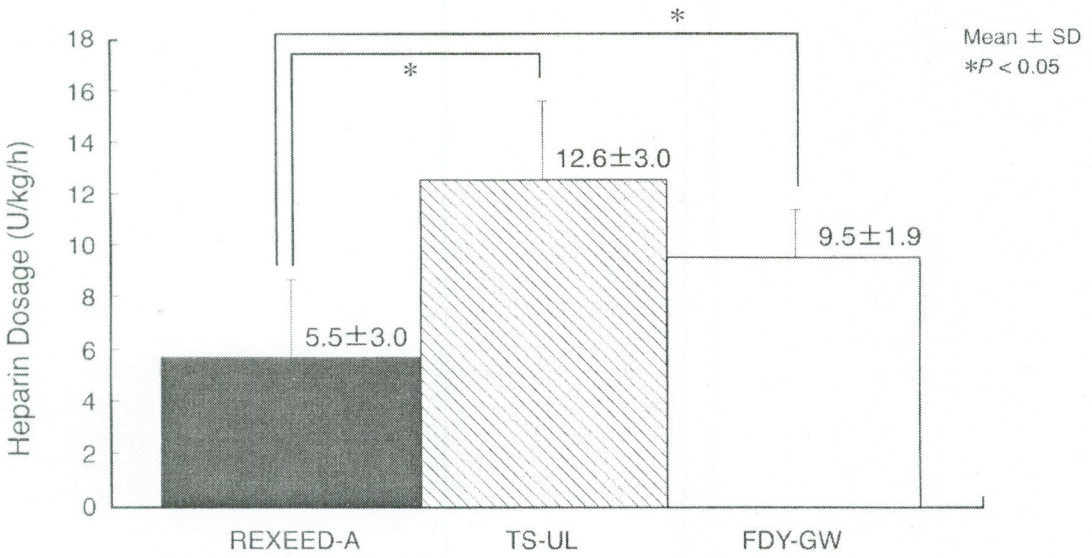

Figure 1. Minimum required heparin dosage for each dialyzer

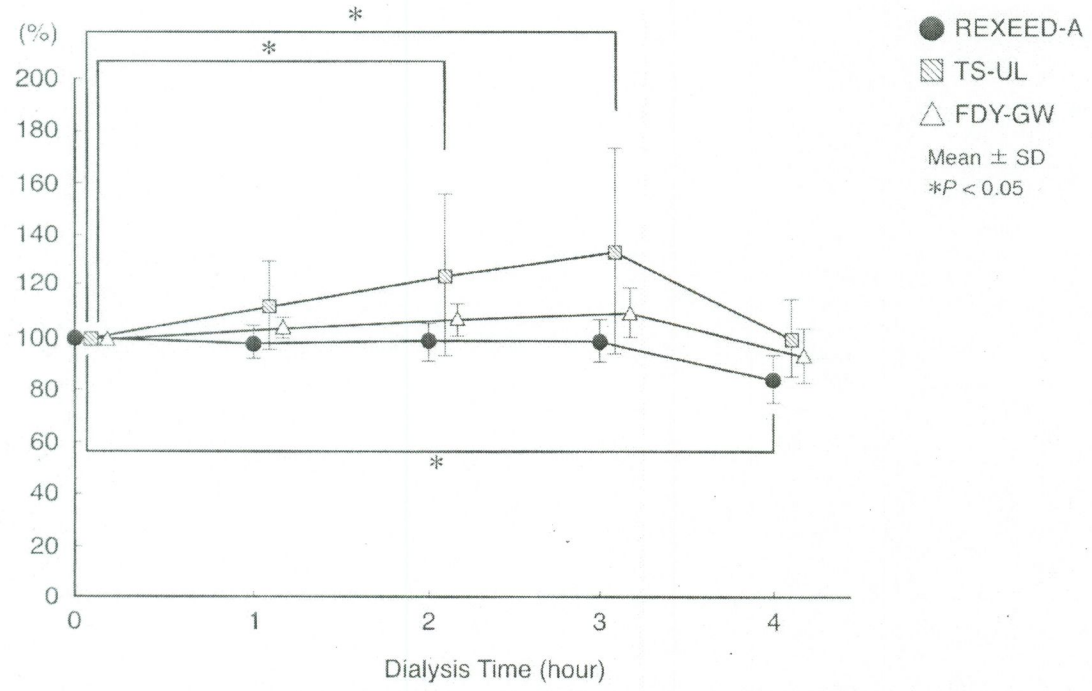

Figure 2. Percent change in activated partial thromboplastin time (APTT) over time (100% being the value at the beginning of dialysis)

In addition to the assessment of the minimum required heparin dosage, the timing of the termination of the continuous administration of heparin was also evaluated using the residual blood level in the dialyzer. The result indicated that REXEED-A allowed the continuous administration of heparin to be concluded 1 hour 30 min prior to the completion of dialysis with the residual blood level at level I (data not shown).

2. Changes in lipids

A significant hourly rise in FFA with respect to pre-dialysis levels was noted for each dialyzer (Fig. 3). A significant hourly drop in TG with respect to pre-dialysis levels was noted for each dialyzer; however, REXEED-A significantly suppressed this effect, particularly from 15 min after the start of dialysis until 3 hours into treatment (Fig. 4). A significant hourly rise in LPL with respect

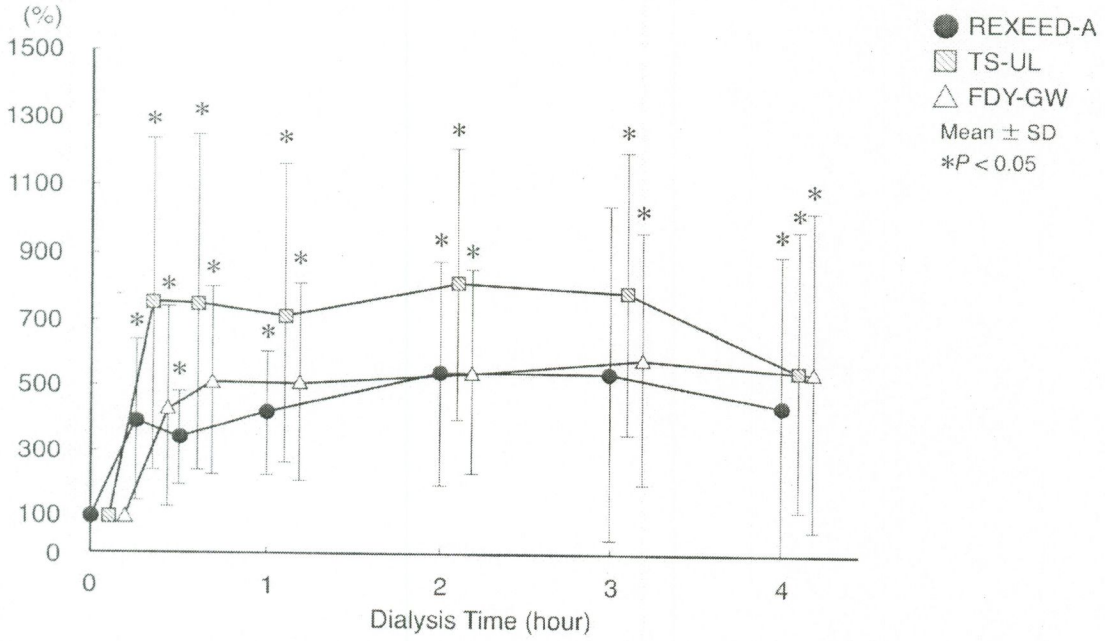

Figure 3. Percent change in free-fatty acid (FFA) over time (100% being the value at the beginning of dialysis)

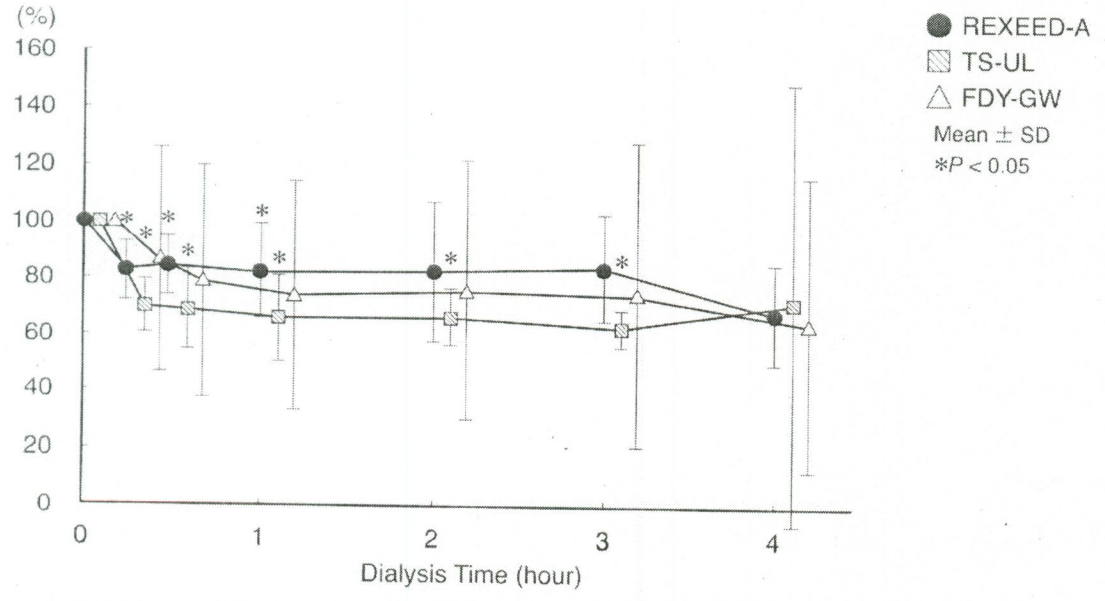

Figure 4. Percent change in triglyceride (TG) over time (100% being the value at the beginning of dialysis)

to pre-dialysis levels was noted for each dialyzer; however, REXEED-A significantly limited the extent of this rise in comparison to TS-UL, particularly at 1 hour after the start of dialysis (Fig. 5).

Discussion

In maintenance hemodialysis, blood coagulation may affect not only the extracorporeal circuit, but also the blood flow in the patient's body. Therefore, the administration of an anti-coagulant is necessary and the appropriate heparin dose is important. However, there are reports of adverse effects as a result of heparin administration [3]. In order to prevent future complications with long-term dialysis and improve treatment outcomes, the action of heparin should be seriously considered along with the biocompatibility of the dialyzer. As a consequence, the advantages of a PS membrane dialyzer, which has excellent solute removal performance as well as good biocompatibility including antithrombogenicity, has been noted in recent years, and this membrane is used extensively in clinical settings [4]. Therefore, this work studied the feasability of reducing the impact on lipid metabolism by reducing the heparin dosage with a PS membrane dialyzer.

We firstly consider the issue of dialyzer biocompatibility: one feature of REXEED-A is its ability to perform dialysis with a lower heparin dosage than conventional dialyzers [4]. Similarly, in the current assessment of residual blood, REXEED-A had a lower minimum required heparin dosage than that of TS-UL and FDY-GW. Even with a dialyzer of the same material, the percent change in platelets and PF-4 differs [1], and the use of an anti-coagulant is believed to further complicate the kinetics of the coagulation system. In particular, patients on prolonged dialysis for 10 years or more experience hyper-coagulability, and secondary fibrinolysis accompanying this hyper-coagulable state also increases; it has also been reported that the thrombotic tendency intensifies because fibrinolytic activation by the vascular epithelium decreases [5]. Moreover, the use of anticoagulants may induce risk factors for blood clotting such as heparin-induced thrombocytopenia (HIT) [6]; therefore, a dialyzer should have biocompatibility with antithrombogenicity such that an anti-coagulant is unnecessary. Accordingly, taking advantage of the features of a dialyzer with little residual blood and using the optimal dose of heparin should allow long-term use while delaying the onset of HIT to the maximum extent possible.

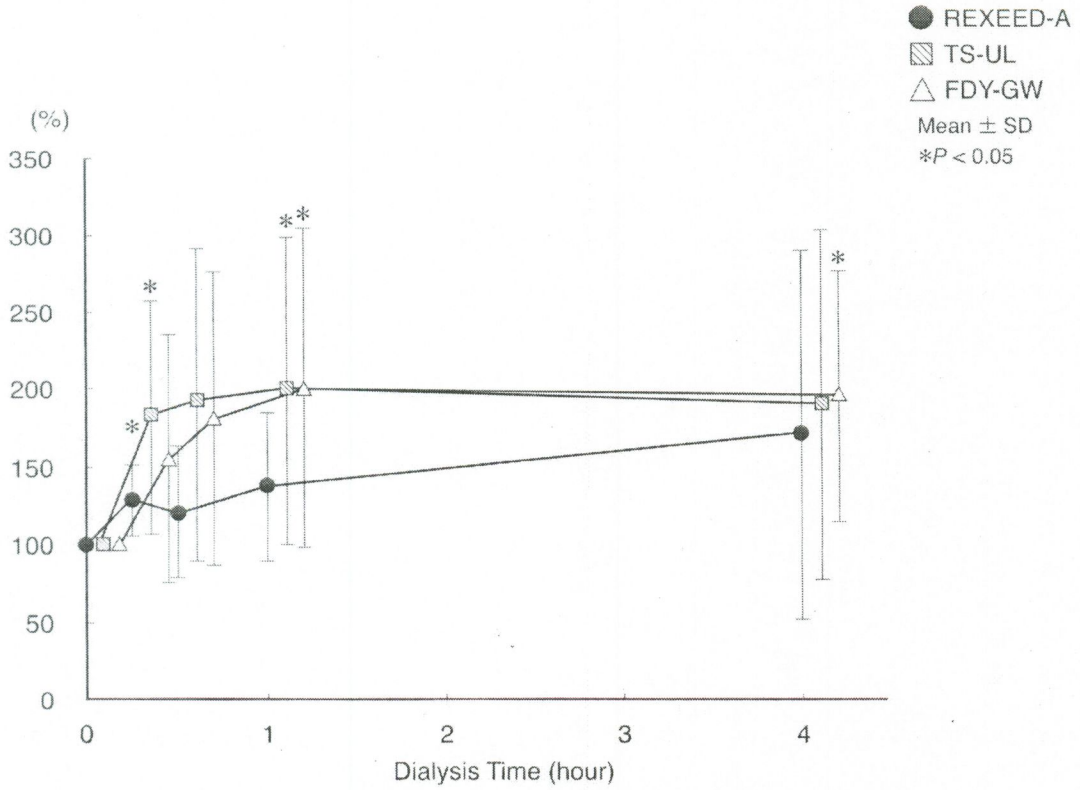

Figure 5. Percent change in lipoprotein lipase (LPL) over time (100% being the value at the beginning of dialysis)

With regard to previous long-term complications for dialysis patients, the effects of heparin on cardiovascular complications and the effects of unfractionated heparin on lipid metabolism have been reported [3]. Another report indicated that in terms of the risk of cardiovascular death, a high level of FFA in blood increases the potential for sudden death [7]. The results of assessing the stimulation of lipids by the minimum required dosage of heparin for a dialyzer indicated that REXEED-A had the lowest required heparin dosage. In comparison to TS-UL and FDY-GW, it limited the increase in FFA and LPL. In particular, REXEED-A suppressed TG most significantly with a percent decrease in TG after 3 hours of dialysis from approximately 15 min after the start of dialysis, when it was almost saturated. With regard to LPL, which regulates TG hydrolysis, one hour after the start of dialysis, REXEED-A was found to significantly limit the extent of the increase in LPL in comparison to TS-UL.

Heparin administration resulted in an increased LPL, inducing the TG hydrolysis and an increase in FFA; however, the increase in each of the two lipids can be limited by reducing the heparin dosage while monitoring the residual blood, APTT, etc. Consequently, using a dialyzer with exceptional antithrombogenicity and maintaining heparin at the optimal minimum dosage during hemodialysis is expected to effectively delay the onset of complications for elderly dialysis patients and long-term dialysis patients at risk of developing cardiovascular complications such as heart failure.

Conclusion

The prevention of long-term complications is linked to limiting the rise in FFA by decreasing the heparin dose through assessing the residual blood in a dialyzer. In the current study, REXEED-A had a satisfactory level of residual blood after dialysis in comparison to other dialyzers, and it also had little impact on lipid metabolism. In the future, long-term continuous assessment must be performed and whether or not REXEED-A is effective in delaying the onset of complications must be verified.

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ASAHI KASEI KURARAY MEDICAL CO., LTD.

9-1, Kanda Mitoshirocho, Chiyoda-ku, Tokyo 101-8482, Japan
TEL: +81-3-3259-7722 FAX: +81-3-3259-5899
http://www.asahikasei-kuraray-medical.com

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