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Introduction

The polysulfone membrane dialyzer REXEED-A* developed by Asahi Kasei Medical Co., Ltd. aims to improve small molecule removal compared to conventional APS dialyzers; this is achieved by means of narrowed and waved hollow fibers and by adopting a new housing with a full baffle at the dialysate inlet/outlet ports in addition to a short taper immediately below the ports. REXEED-15A (REXEED-A) was tested in a clinical environment, and investigated for its solute-removal performance, biocompatibility, and anti-coagulation properties; furthermore, its performance was compared with that of the PEPA membrane dialyzer FDY-150GW (FDY) and PES membrane dialyzer PES-150DS (PES).

Subjects and Methods

Six patients (3 male, 3 female) receiving stable maintenance dialysis for 4 hours three times per week in our hospital provided informed consent to participate in the investigation (Table 1). Their

Table 1. Subjects and methods

Subjects:	Six patients on stable maintenance dialysis (3 male and 3 female)
	Age (mean ± SD): 63.3 ± 8.6 years
	Years on dialysis (mean ± SD): 6.2 ± 3.1 years
	Body weight (mean ± SD): 52.3 ± 11.2 kg
	Primary cause for dialysis: chronic glomerulonephritis in four cases
	diabetic nephropathy in two cases
Methods:	Each dialyzer used in a 2-week crossover design
	Blood samples collected on second dialysis in week
Evaluation items:	
	Clearance and reduction ratio
	Small molecules: BUN, Crea, UA, iP
	Low molecular weight proteins: β_2m, α_1m
	Albumin loss
	Loss was calculated based on total pooling of waste dialysate
	Biocompatibility
	WBC, Plt, C3a (0 min from arterial and 15, 30, 60, and 240 min from venous side)
	Coagulation parameters and residual blood
	TAT (0 min from arterial and 30, 60, and 240 min from venous side)
	Residual blood score visually assessed on a scale ranging from 1 = 0% up to 5 = 100% at intervals of 0.5

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

Table 2. Specifications

	REXEED-A	FDY	PES
Membrane material	PS	PEPA	PES
Effective surface area (m^2)	1.5	1.5	1.5
Internal diameter (μm)	185	210	200
Wall thickness (μm)	45	30	30
Priming volume (mL)	82	91	93
Sterilization	γ -ray	γ -ray	γ -ray
Dry/Wet	Wet	Wet	Dry

PS: Polysulfone, PEPA: Polyester Polymer Alloy, PES: Polyethersulfone

mean age was 63.3 ± 8.6 years; mean years on dialysis, 6.2 ± 3.1 years; and mean body weight, 52.3 ± 11.2 kg (expressed as mean ± standard deviation). The primary reason for dialysis was chronic glomerulonephritis in four cases and diabetic nephropathy in two cases, with no particular complications. Three types of dialyzers were used in a two-week crossover design. Table 2 lists the specifications of the dialyzers.

With regard to solute removal, the three dialyzers were compared in terms of the clearance (1-hour value) and reduction ratios of small molecules and low molecular weight proteins. Blood urea nitrogen (BUN), creatinine (Crea), uric acid (UA), and inorganic phosphate (iP) were selected as small molecules. β_2-microglobulin (β_2m) and α_1-microglobulin (α_1m) were selected for analysis as low molecular weight proteins.

In order to evaluate albumin loss, all waste dialysate was collected and pooled for analysis. In addition, measurement and calculation of solute removal were performed according to The Performance Evaluation Method for Blood Purification Devices [2] stipulated by the Japanese Society for Dialysis Therapy.

For biocompatibility markers, white blood cell (WBC) count, platelet (Plt) count, and complement C3a (C3a) concentration were measured by collecting blood samples from the arterial side of the dialyzer at the start of dialysis as a reference value, and from the venous side of the dialyzer at 15, 30, 60, and 240 min after the start of dialysis. The values were then transformed into a relative rate against the reference values.

For markers of the coagulation system and anticoagulation properties, thrombin-antithrombin III complex (TAT) was measured by collecting blood samples from the arterial side of the dialyzer at the start of dialysis and from the venous side of the dialyzer at 30, 60, and 240 min after the start of dialysis. In addition, the residual blood level at the circumference of the fiber bundle and the header cap areas was checked visually after dialysis to record and evaluate a residual blood score for each dialyzer using our hospital standard scale where 1 = 0% and 5 = 100%, graduated in intervals of 0.5.

A dialysis machine manufactured by Nikkiso Co., Ltd. was used for all treatments. The endotoxin (ET) concentration in the dialysate in the distal portion of the dialyzer was monitored, and the result showed that the level was below the detection limit at each evaluation. The blood sampling was made on the second dialysis day in the week, and statistical analyses were performed using Student t-test with a P value below 5% defined as being statistically significant.

Results

1. Clearance

REXEED-A exhibited a very high clearance value of 195.2 ± 1.5 mL/min for BUN with statistical significance compared to the other two dialyzers (Fig. 1). For Crea, REXEED-A and FDY exhibited significantly higher values than PES. For UA and iP, REXEED-A exhibited a significantly higher value than the other two dialyzers, and FDY also exhibited a significantly higher value than PES.

For low molecular weight proteins, REXEED-A exhibited clearance values of 58.4 ± 5.8 mL/min and 10.9 ± 4.1 mL/min for β_2m and for α_1m, respectively, without statistical significance compared to the other dialyzers.

2. Reduction ratio and albumin loss per session

For the reduction ratio of small molecules, REXEED-A exhibited a significantly higher difference in iP compared to PES (Fig. 2). In addition, for low molecular weight proteins, the ratios were 67.6% ± 4.7% and 5.5% ± 4.5% for β2m and α1m, respectively, with a statistical significance in the β2m reduction ratio compared to the other dialyzers.

The albumin loss per session was 0.49 ± 0.11 g, 1.06 ± 0.46 g, and 1.79 ± 0.27 g for REXEED-A, FDY, and PES, respectively. This result showed that REXEED-A had a lower albumin loss compared to the other dialyzers with statistical significance.

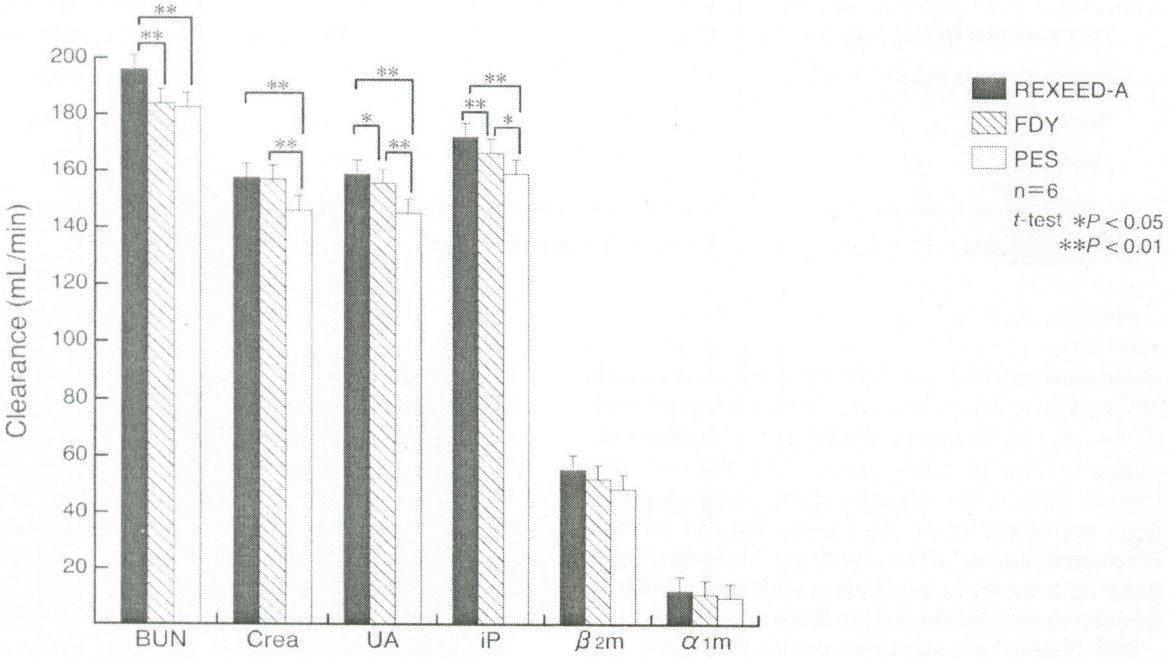

Figure 1. Clearance
QB = 200 mL/min, QD = 500 mL/min
β2m and α1m : corrected by hematocrit value

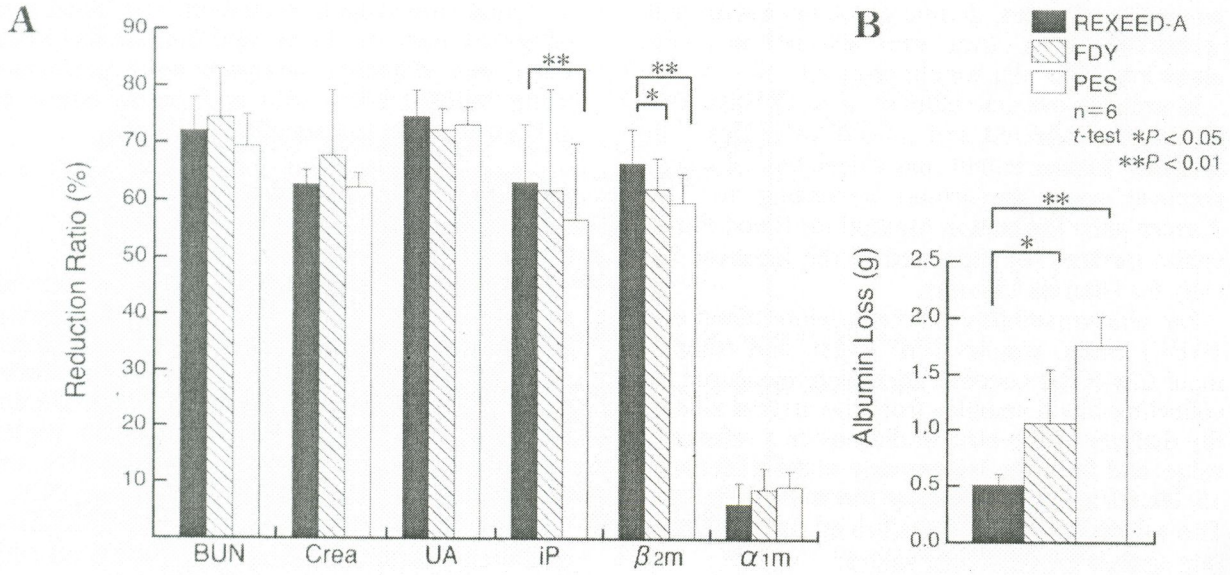

Figure 2. Reduction ratio (A) and albumin loss per session (B)
QB = 200 mL/min, QD = 500 mL/min
β2m and α1m: corrected by hematocrit value

3. Biocompatibility

With regard to the change in the WBC count during the session, REXEED-A had a smaller change after 15 min of dialysis compared to PES with statistical significance (Fig. 3). No significant difference was observed in the change in the Plt count.

With regard to complement activation, REXEED-A exhibited a lower C3a value with a significant difference compared to FDY and PES after 30 and 60 min of dialysis, respectively. However, all the dialyzers exhibited a tendency to return to the reference values at the end of dialysis.

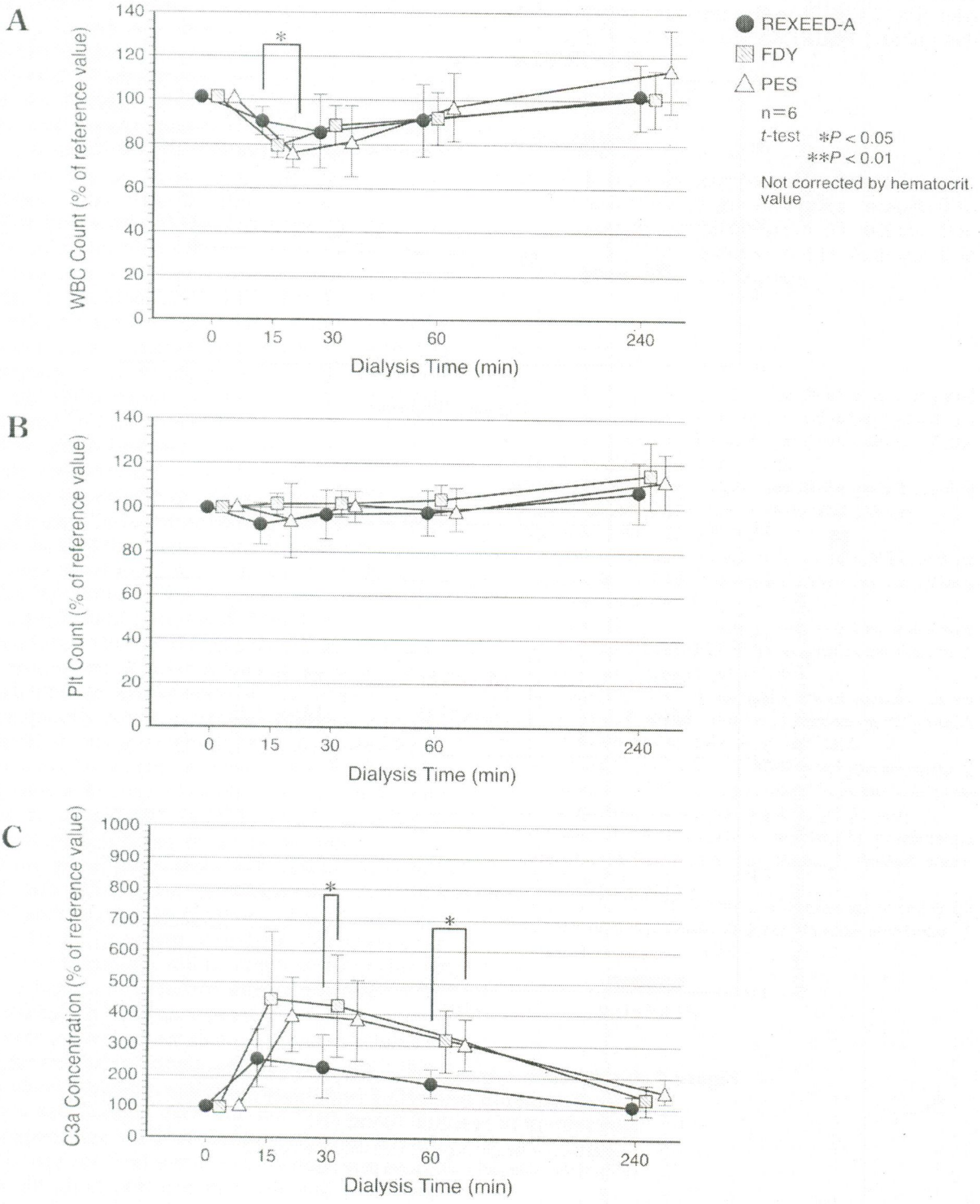

Figure 3. Biocompatibility: WBC (A), Plt (B), and C3a (C)

4. Coagulation system and anti-coagulation properties

TAT remained low in each dialyzer and no significant difference was observed (Fig. 4). With regard to the visual evaluation at recovery, there was no remarkable residual blood and the residual blood scores were good for all dialyzers.

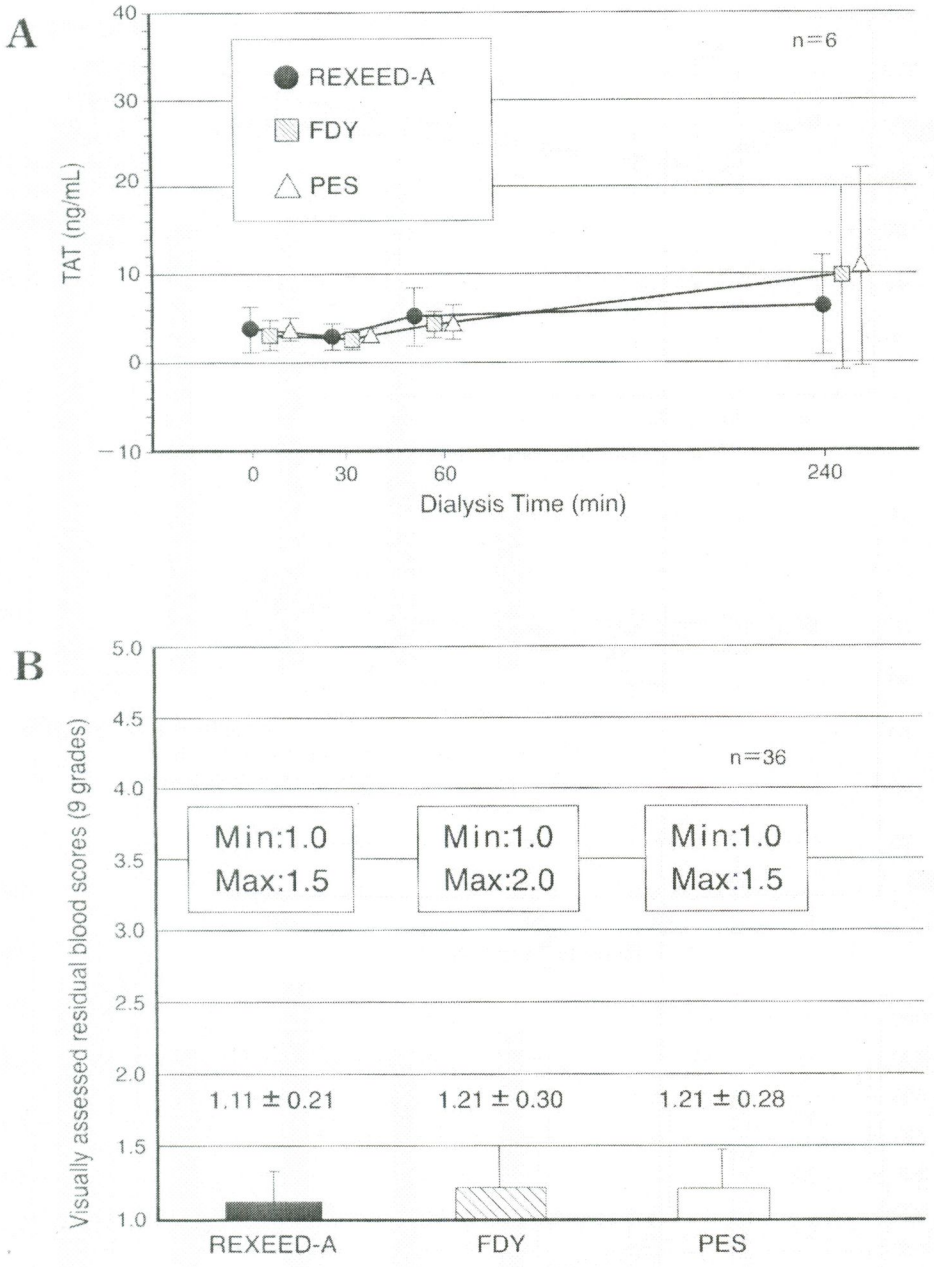

Figure 4. Coagulation system evaluated by TAT (A) and anti-coagulation properties evaluated by visual assessment of residual blood (B)

Low molecular weight heparin: 1833 units (two cases)
Unfractionated heparin: 3000 units (four cases)

Discussion

REXEED-15A displayed excellent removal of small molecules due to the improved dialysate flow at the inlet port. Moreover, the REXEED-A has wave-shaped hollow fibers which result in a lower fiber density in the dialyzer casing when compared with conventional products. This lower fiber density is believed to generate a smaller internal filtration volume during dialysis, however, REXEED-A maintained a high removal of the low molecular weight protein β2m. Since both diffusion and filtration may affect the removal of low molecular weight proteins such as β2m, there was a possibility that enhanced diffusion compensated for the decrease in internal filtration. Furthermore, narrowing the internal diameter of the hollow fibers might also influence the improvement in removal performance. However, these mechanisms could not be elucidated in this study. In addition, since REXEED-A exhibited a low albumin removal ($\leq$0.5 g/session), it may be a better option, particularly in cases where it is necessary to avoid albumin loss [2]. However, the molecular cut-off point could not be properly evaluated in this study because neither myoglobin nor prolactins were measured. Further studies are required to resolve these issues.

During the course of dialysis using REXEED-A, the changes in biocompatibility parameters were small, so that the in vivo stimulus was believed to be suppressed to a low level as well. With regard to the biocompatibility, there is a possibility that the complement proteins activated by contact between blood and the dialysis membrane stimulate the production of inflammatory cytokines such as interleukin or tumor necrosis factor (TNF) and consequently result in various complications [3]. In addition, in cases where large pore-sized membranes are used, the possibility that ET from the dialysate side may back-filter to the blood side must be considered [4]. Therefore, in order to prevent or minimize these possibilities, clinical staff are required to test for dialysate purity and fluid path disinfection and cleanliness on a daily basis and to provide dialysate of relatively high purity [5, 6]. However, it is debatable whether or not these measures will be taken in every clinical site in Japan in the future without the addition of related health insurance points.

Therefore, we expect that every manufacturer of dialysis-related products will develop and utilize less bio-stimulatory materials and dialyzer membranes with less ET back filtration [7,8]. Moreover, we expect the early realization of safer, easier, and better medical services implementing an ET back filtration performance test and promoting the establishment of its evaluation method.

For coagulation system and anti-coagulation properties, although the dialyzer fibers are both waved and of smaller internal diameter, REXEED-A could be used in a manner similar to conventional APS dialyzers since it displayed good anti-coagulation properties with no marked increase in TAT, and it exhibited no detrimental effects under the dosage of coagulant used in this study. In addition, the use of REXEED-A is also preferable because of the decreased priming volume.

Conclusion

REXEED-A is a dialyzer with an enhanced removal performance for small molecules compared to the conventional APS dialyzer. We believe that REXEED-A is a highly versatile dialyzer that will be useful in clinical practice.

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