



eli·io
POLYNEPHRON™

Research Program Overview

ELISIO™ POLYNEPHRON™:

Confidence From The Inside Out

By combining more than 30 years of global experience in design and manufacture of dialyzers with extensive research and engineering innovation, Nipro created the ELISIO™ Polynephron™ Single Use, Hollow-Fiber Dialyzer. This state-of-the-art product evolves and advances our extensive fiber and dialyzer manufacturing expertise to your benefit. The result: state-of-the-art performance through a synthesis of a remarkable new membrane material and significant design improvements.

Numerous clinical studies have been done using ELISIO dialyzers. The results show that usage of ELISIO dialyzers lead to:

- Improved low molecular weight protein removal
- Improved hemoglobin outcomes
- Decrease in ESA (Erythropoiesis Stimulating Agent) doses administered
- Reduction in EPO resistance index
- Lower coagulation activation





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Evaluation of the new Nipro ELISIO™-17H in comparison with two reference filters

Introduction

The Nipro ELISIO™-17H dialyzer is equipped with a new synthetic high-flux dialysis membrane named POLYNEPHRON™. It is characterized by an optimized removal for small molecules as well as for low-molecular weight (LMW) proteins, while retaining albumin.

This dialyzer features a new polypropylene housing and headers and is completely Bisphenol-A free. The purpose of this evaluation was to evaluate the biocompatibility, the thrombogenicity and the clearance properties in hemodialysis in comparison with 2 reference dialyzers.

Methods

Eight stable dialysis patients (4M+4F; mean age 62±13-16) underwent one week of 3 consecutive HD treatments with each dialyzer type (ELISIO™-17H [POLYNEPHRON™; Nipro Corporation, Japan; 1,7 m²]; FX80 [Helixone®; Fresenius Medical Care AG, Germany; 1,8 m²]; Polyflux® 170H [referred as GP170H; Polyamix®; Gambro Lundia AB, Sweden; 1,7 m²]). Blood and dialysate flow rates were set at 300 and 500 mL/min respectively, the UF rate was as prescribed by the physician. Pre-rinsing was performed with 1000 ml of saline. Blood samples were collected at appropriate time intervals for the evaluation of performance and hemocompatibility. Whole blood clearances and removal rates (RR) of small solutes (urea, creatinine, phosphate), LMW proteins (β_2 m, 11,800 Da and myoglobin, 17,800 Da) and albumin (66,000 Da) as well as hemocompatibility parameters (WBC, platelet count, C5a, pmn-elastase, thrombin-antithrombin III [TAT]) were measured. After treatment, the dialyzers were intensively rinsed by means of RO water from the dialysate to the blood side (pressure 1-2 bar) and the number of irreversibly clotted fibers was visually estimated thru the surface of the dialyzers. Data analysis was done using Microsoft Excel software. All parameters are given as mean and standard error of measurements. Differences between results were tested using the Student's t-test or U-test (Mann-Whitney).

Results

Clearances for β_2 m and myoglobin were significantly higher with the ELISIO-17H than with the GP170H and the FX80 (Fig. 1). Removal rates (RRs) for the small molecules (urea, creatinine, phosphate) did not differ significantly between the dialyzers. For the RRs of the larger molecules (β_2 m and myoglobin), the ELISIO-17H was superior to the other 2 dialyzers (not shown). None of the dialyzers led to a measurable RR for albumin (66,000 Da). The biocompatibility parameters (WBC Count and C5a) were not different for the three dialyzers. PMN elastase was comparable for ELISIO and FX80, but larger for GP170H. Thrombogenicity parameters were also analyzed. No significant differences in platelet count were found between the dialyzers. There was a small but significant increase in TAT during dialysis for all dialyzers, but this increase tended to be the smallest for the ELISIO. Permanently clotted fibers on the dialyzer surface were counted and judged by means of a grading. The ELISIO-17H showed the smallest number of such permanently clotted fibers. The ELISIO-17H can be regarded to have a significantly lower thrombogenicity compared with the GP170H.

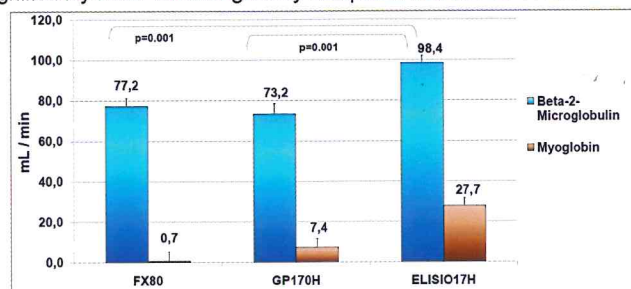


Figure 1: Clearances of β_2 m and myoglobin at QB=300 mL/min (means of 30 and 180 min values). Mean values \pm standard errors are given. Values for ELISIO were higher compared with both references.

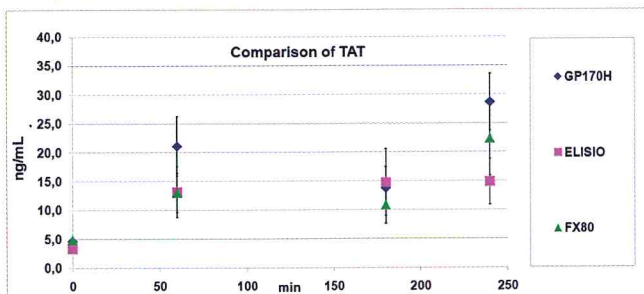


Figure 3: Time course of thrombin-antithrombin-III complex (TAT) during HD. For all dialyzers, the TAT increase at 4h was significant, but no statistical differences between dialyzers could be detected. However, the ELISIO-17H tended to have the smallest increase in TAT, the GP170H the highest.

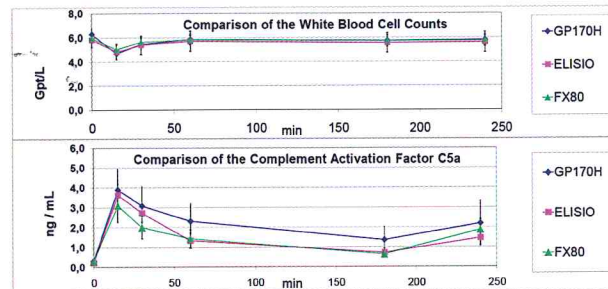


Figure 2: All dialyzers showed a mild WBC drop with a maximum at 15 min, concomitant with an increase in complement factor C5a. These parameters were in a range that is typical for synthetic biocompatible membranes and were not different between the three dialyzers.

grading:	
red fibers	grade
0...10	1
11...20	2
21...50	3
51...100	4
>100	5

Patient	GP170H 17/02/2010	ELISIO-17H 24/02/2010	FX 80 3/03/2010
	grade	grade	grade
HW	3	1	2
AS	2	1	1
MB	5	4	4
EM	3	2	1
RW	5	5	5
KB	4	3	3
BG	3	1	1
WW	5	1	5
mean:	3,8	2,3	2,8

Figure 4: Estimation of permanently clotted fibers: fibers were visually examined for clotting and 5 grades were distinguished. The GP170H had the largest number of clotted fibers, followed by the FX80.

Conclusion

Concerning the small molecule clearance data, the ELISIO-17H proved superior to the FX dialyzer. For larger molecules (β_2 m and myoglobin), the ELISIO-17H was significantly more efficient than the Polyflux 170H and the FX80. Similarly, the removal rates for β_2 m and myoglobin proved the superiority of the ELISIO-17H. For all dialyzer types, no RR of albumin was detected under the HD conditions used.

Concerning hemocompatibility, no significant differences were observed between the three dialyzers studied with respect to the WBC counts and complement activation. The activation of pmn-elastase was comparable for the ELISIO-17H and the FX80, but larger for the Polyflux 170H. The thrombogenicity judged by platelet count, TAT and the estimation of residual blood was the lowest for the ELISIO, whereas the Polyflux showed a comparatively higher thrombogenicity.

Clinical Performance of the Nipro ELISIO™-190H Dialyzer in Hemodialysis and Hemodiafiltration

Introduction

The Nipro ELISIO™-190H dialyzer is equipped with a new synthetic high-flux dialysis membrane named POLY-NEPHRON™. It is characterized by an optimized removal for small molecules as well as for low-molecular weight (LMW) proteins. *In vitro* studies have indicated that the performance of the Nipro ELISIO™ 190H dialyzer must be superior to conventional high-flux filters. In a first clinical trial, this new dialyzer was compared to two reference filters. Its suitability for hemodialysis (HD) and online postdilution hemodiafiltration (HDF) was tested.

Methods

In a prospective, randomized, cross-over study on eight maintenance dialysis patients (all male; age 56 ± 12 years), the Nipro ELISIO™-190H dialyzer (referred as NE; Nipro Corporation, Japan; 1.9 m^2) was compared to the two synthetic high-flux reference dialyzers Fresenius FX80 (referred as FX; Helixone® (polysulfone), Fresenius Medical Care AG; 1.8 m^2) and Gambro Polyflux® 170H (referred as GP; Polyamix®, Gambro Hechingen; 1.7 m^2). Each patient underwent three HD and three online postdilution HDF treatments. Blood and dialysate flow rates were set at 400 and 700 mL/min, respectively. In HDF, the substitution flow rate was set at 80 mL/min resulting in an effective dialysate flow rate of 620 mL/min. The treatment time was 240 ± 0 min. During each third HD and HDF treatment, instantaneous plasma clearances (K) and reduction rates (RR) of small solutes (urea, creatinine, phosphate) and LMW proteins ($\beta_2\text{m}$, 11,800 Da; cystatin c, 13,400 Da; myoglobin, 17,800 Da; retinol-binding protein, 21,200 Da; α_1 -microglobulin, 30,000 Da) as well as biocompatibility parameters (WBC, platelets, C5a, thrombin-antithrombin III (TAT)) were measured. The albumin (67,000 Da) loss was determined in continuously collected dialysate. For statistical analysis, a two-way ANOVA was performed.

Results

K for small solutes (urea, creatinine, phosphate) were not statistically different between the dialyzers. For the LMW proteins $\beta_2\text{m}$ (Figure 1), cystatin c and myoglobin (Figure 2 and 3), compared to FX and GP, NE obtained by far higher instantaneous plasma clearances at 30 and 180 min as well as reduction ratios in both therapy modes. With higher molecular weight, the differences between NE and the references increased. None of the dialyzers led to clinically considerable removal of retinol-binding protein or α_1 -microglobulin. The albumin loss was slightly higher with NE being 0.52 ± 0.13 in HD and 1.61 ± 0.63 g in HDF (FX and GP in HD 1.15 ± 0.38 and 1.42 ± 0.24 g). The biocompatibility parameters were excellent and not different for the three dialyzers. Only a typical minor leukocyte drop (Figure 4) and complement C5a increase was observed between 5 and 10 min for all dialyzers. There was virtually no activation of coagulation as indicated by low and stable TAT values.

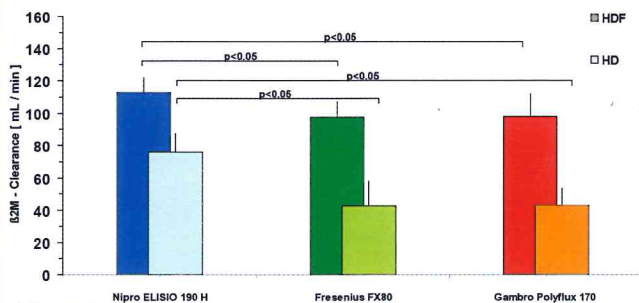


Figure 1: Instantaneous plasma clearances of $\beta_2\text{m}$ at 30 min. Mean values \pm standard deviation are given. Values for NE in HD and HDF were higher compared with both references. No difference between FX and GP.

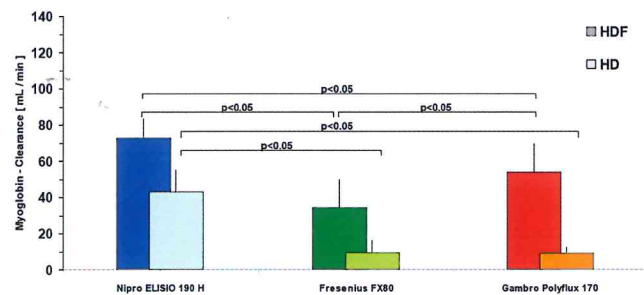


Figure 2: Instantaneous plasma clearances of myoglobin at 30 min. The figure depicts mean values \pm standard deviation. NE was by far superior to both references in HD and HDF. FX performed lower than GP in HDF.

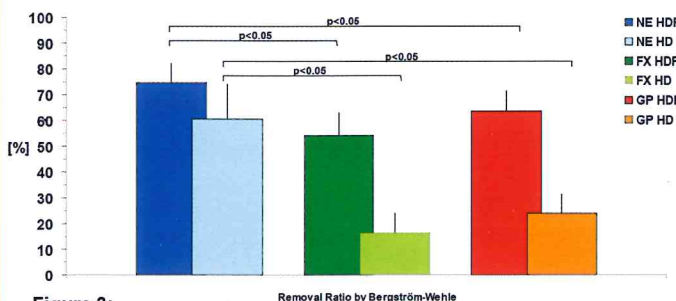


Figure 3: Removal rates of myoglobin (17,800 Da) corrected for hemoconcentration. Mean values \pm standard deviation are shown. NE was superior to FX and GP in both HD and HDF. In HD, the removal rate of NE was on the level of HD with the conventional filters FX and GP.

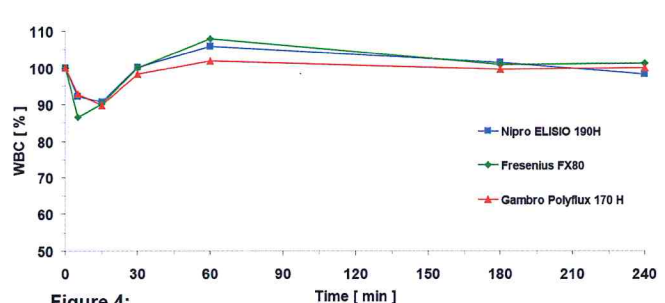


Figure 4: Course of the total leukocyte count during HD relative to baseline. After reaching a typical nadir between 5 and 10 min, the values returned to about baseline after 60 min. There was no difference between the three dialyzers.

Conclusion

In this first clinical trial, the new Nipro ELISIO™-190H dialyzer was easy to handle and showed perfect suitability for both HD and HDF. Independently of the treatment mode, it demonstrated much better performances than the reference filters with regard to LMW protein removal. This superiority in LMW protein removal was not at the expense of albumin loss, which, indeed, was higher than FX

and GP but remained by far within clinically accepted limits. The biocompatibility parameters were in the typical range for a modern synthetic dialyzer and must be regarded as excellent. The performance of the new ELISIO™ dialyzer can be considered as a contribution to more adequate dialysis and its chronic use may have beneficial effects on patient outcome.

Consequences on Renal Anemia of Two Synthetic High-Flux Dialyzers

Introduction

Membrane biocompatibility and performance have long been thought to be relevant to renal anemia. This study compared the consequences on renal anemia of 2 synthetic high-flux dialyzers during 6 months. Optimal renal replacement therapy could play a role in correcting the anemia by removing small and possible medium-to-large molecules that inhibit erythropoiesis. The 2 dialyzers were a standard polysulphone dialyzer (HF80S) and the ELISIO™-190H dialyzer, based on the new Polynephron™ membrane. We wanted to evaluate the anemia improvement effects in both dialyzer groups.

Methods

In a prospective, randomized study on twenty maintenance dialysis patients (11 male; 9 female; mean age: 72 years), the Nipro ELISIO™-190H dialyzer (referred to as ELISIO; Nipro Corporation, Japan; 1.9m²) was compared to a synthetic high-flux reference dialyzer HF80S (referred to as HF), polysulfone, Fresenius Medical Care AG, 1.8 m². Ten patients were treated for 6 months with the ELISIO dialyzer and the other ten with the HF. There were 2 dropouts in each group. Each patient underwent three HD treatments per week. Blood and dialysate flow rates were set at 400 and 700 mL/min, respectively. The treatment time was 240±21.9 min. At T=0 and then every month, during each third HD treatment, instantaneous plasma clearances and reduction rates of small solutes (urea, creatinin, phosphate), pre-dialysis levels of β_2 -microglobulin (11.800 Da), hematological parameters (haemoglobin level, haematocrit), serum iron, TIBC, and ferritin were measured. The anemia improvement effects were evaluated by calculating the ESA doses and the EPO Resistance Index.

Results

Kt/V increased between T0 and T6 (after 6 months) in both groups but the increase was not significant (not shown). β_2 -microglobulin pre-dialysis levels decreased significantly between T0 and T6 in both dialyzer groups (see table 1). The haemoglobin levels increased between T0 and T6 (Fig. 1); this increase was significant ($p=0.006$) only for the ELISIO-group. ESA (Erythropoiesis Stimulating Agent) did not change significantly during the 6-month period (Fig. 2). The EPO Resistance index decreased by 22.7% between T0 and T6 in the ELISIO-group and increased by 14% in the HF-group, but these changes were not statistically significant (Fig. 3).

Table 1: Pre-dialysis β_2 -microglobulin levels at T0 and T6 in ng/mL. Mean values \pm standard deviation are given. The levels decreased significantly after 6 months.

β_2 -microglobulin pre-dialysis levels				
	HF	Elisio	p	Diff.
n°	7	8		
T0	42.6 \pm 17.7	28.0 \pm 9.1	0.061	14.6 \pm 7.1
T6	12.7 \pm 6.6	9.9 \pm 4.8	0.36	2.8 \pm 2.95
p	0.001*	0.0000*		
Diff.	29.9 \pm 7.14 (- 70.2%)	18.1 \pm 3.61 (- 64.6%)	0.001*	11.8 \pm 2.9

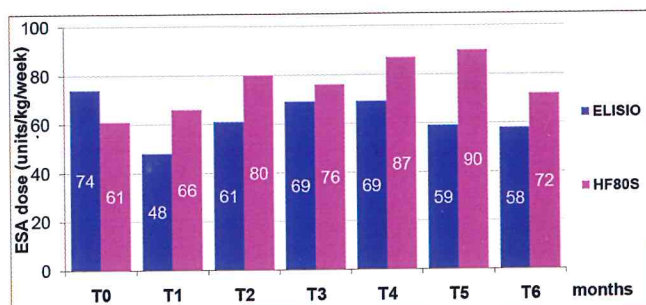


Figure 2: ESA (Erythropoiesis Stimulating Agent) dose administered, in units/kg/week, at T0 until T6. The ESA/kg/week levels are not significantly different. However, ESA doses showed a tendency to increase for the HF group and tended to decrease in the ELISIO group.

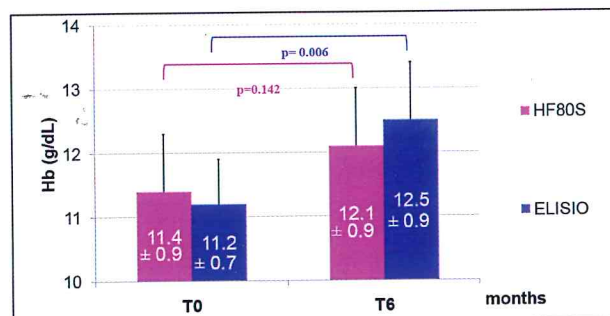


Figure 1: Hemoglobin levels in g/dL at T0 and T6. Mean values \pm standard deviation are given. The increase is statistically significant in patients treated with the ELISIO-dialyzer ($p=0.006$).

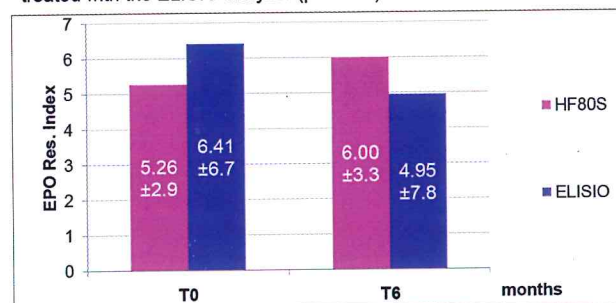


Figure 3: EPO Resistance Index: For the ELISIO-group, there is a reduction of 22.7 % in EPO resistance index. For the HF80S, there is an increase of 14.0% in EPO resistance index. The differences between T0 and T6 are not statistically significant.

Conclusion

Haemoglobin outcome improved overall during the study; the improvement after 6 months was significant for the ELISIO-group only. ESA dose was not significantly different after 6 months compared to baseline in either group. The same holds for the EPO Resistance Index, although a 22.7% decrease was observed in the ELISIO-group and a 14% increase in the HF group.

Do Dialyzers Designed for Increased Internal Filtration Cause Increased Platelet Activation and Thrombin Generation?

Introduction

Middle molecule retention has been reported to reduce survival for long term haemodialysis patients. To increase middle molecule clearances, such as β_2 -microglobulin, high flux dialyzers with increased internal filtration have been developed. However increased internal filtration may increase the risk of dialyzer clotting due to haemoconcentration and loss of anticoagulant. To investigate this possibility, we studied plasma markers of coagulation, platelet, white cell and endothelial activation during dialysis sessions with ELISIO 210H and FX100, dialyzers developed to increase internal filtration.

Methods

15 patients (53.3% male; age 66.1 ± 2.1 years) attending for thrice weekly outpatient hemodialysis (HD) who had been dialyzing with polysulphone and polyvinylpyrrolidone (PVP) dialyzers (Helixone®, FX100, Fresenius, Bad Homburg, Germany) were studied during a midweek dialysis session and then after 12 weeks of HD with polyethersulphone and PVP dialyzers (Polynephron™, ELISIO -210H, Nipro Corporation, Osaka, Japan). Measured mean blood flow rates were 288 ± 5.4 ml/min (FX100) vs 285.5 ± 3.7 ml/min (ELISIO). Dialysate flow was maintained at 800 ml/min. The treatment time was 4.16 ± 0.07 hours. 12 patients were anticoagulated with LMWH (Tinzaparin®), mean dose 2464 ± 383 IU vs 2643 ± 372 IU, administered into the venous limb of the circuit, two patients used no anticoagulant and one patient lepirudin. Both the dialysers and venous air detector chambers were observed during and at the end of the dialysis session for presence of clot formation, and assessed by a visual analogue scale. In addition to standard investigations (coagulation screen, full blood count and albumin level), Tinzaparin® levels, factor (F) VIII:C, von Willebrand factor antigen (VWF:Ag), VWF propeptide (VWFpp), thrombin anti-thrombin (TAT) complexes, prothrombin fragment 1+2 (F1+2) and D-dimers were measured. Thrombin generation assays were carried out on double spun plasma triggered with 5pM reagent using the calibrated automated thrombogram (CAT) method. The endogenous thrombin potential (ETP) was generated by dedicated software. The CTAD plasma samples were used for the measurement of platelet activation markers (b-thromboglobulin (b-TG), platelet factor 4 (PF4) and soluble (s) sP-selectin. Plasma levels of the following adhesion molecules were determined by ELISA: soluble (s) CD40 ligand, sICAM-1, sVCAM-1 and sE selectin. Results are expressed as mean \pm standard deviation, or median and interquartile range, or percentage. Statistical analysis was by students' paired t test for parametric data and by the Wilcoxon rank sum pair test for nonparametric data, with Bonferroni correction where appropriate.

Results

1. All dialysis sessions were completed satisfactorily, with no significant clotting. External examination of the dialyzers did not show any clotting in the outer fibres or header, and no clot formed in the venous air detector.
2. Routine laboratory clotting tests (PT, APTT and TT) did not change significantly with dialysis, and were not different between the two dialyzers.
3. At the start of dialysis, patients had evidence of activation of coagulation (with increased factor VIII:C, VWF:Ag, VWF:pp, TAT and F1+2), and evidence of increased fibrinolysis (raised D-dimers).
4. Coagulation activation, as measured by TATs and F1+2, at the end of the dialysis session was less with the ELISIO dialyzer than with the FX dialyzer. (see Fig. 1 and 2)
5. There was no difference in Tinzaparin® levels at end of dialysis session using either dialyzer, as shown by anti-Xa activity - 0.145 ± 0.027 IU/ml (FX) vs 0.11 ± 0.017 IU/ml (ELISIO), showing that there were no significant LMWH losses during the treatment.
6. Prior to dialysis, patients showed evidence of platelet activation with increased PF4 and b-TG levels. However, PF4 and b-TG levels did not increase further with dialysis, or with either dialyzer, but plasma sP-selectin did increase with dialysis suggesting platelet activation, as P-selectin is released from intracytoplasmic platelet granules.
7. Dialysis was associated with the release of soluble platelet integrin (sP selectin) and increased endothelial activation with increased levels of VWF:Ag, VWF:pp and sE selectin.

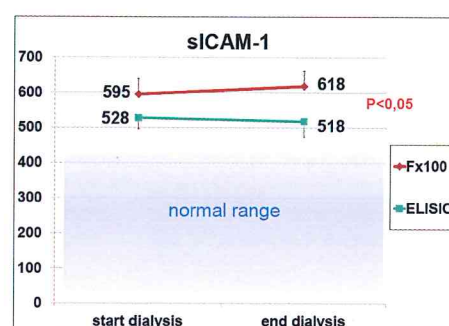
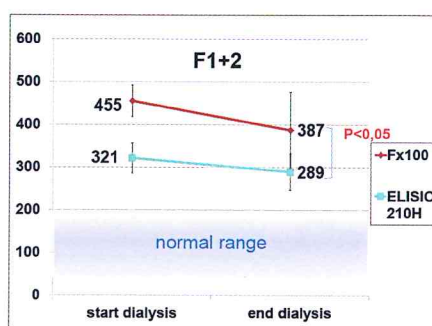
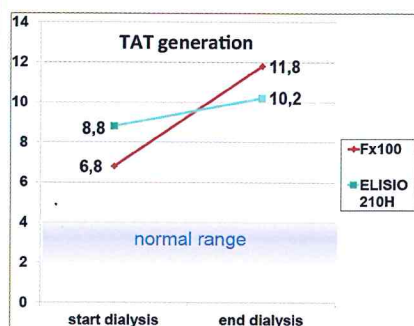


Figure 1 and 2:

TAT levels (median in $\mu\text{g/L}$) and F1+2 levels (mean \pm SEM in pmol/L) at the start and at the end of a treatment. The increase was significantly lower for the ELISIO compared to the FX100.

Figure 3:

sICAM-1 levels (in ng/mL) at the start and at the end of a treatment

Conclusion

All dialysis sessions were completed satisfactorily with no significant clotting. Despite adequate dialysis ($\text{Kt/V } 1.47 \pm 0.06$), haemodialysis patients have an inflammatory phenotype, characterized by increased activation of coagulation, platelets and fibrinolysis, but the dialyzers did not significantly increase platelet activation or thrombin generation. There was no difference in anti Xa activity at the end of the dialysis session with the membranes, suggesting that there was no additional loss of low molecular weight heparin with the ELISIO and the FX dialyzers. Coagulation activation, as measured by TATs and F1+2, at the end of the dialysis session was less with the ELISIO dialyzer. Dialyzers designed to increase internal filtration and convective transport did not significantly lead to increased LMWH losses or increased risk of thrombosis.

Influence of the Nipro ELISIO™-190H on the Proinflammatory Activity of Circulating Mononuclear Cells

Introduction

The objectives of this prospective, randomized and comparative study (in two parallel groups) were to compare the Nipro ELISIO™-210H dialyzer between hemodialysis (HD) and on line hemodiafiltration (HDF) techniques in terms of different parameters including dialysis efficacy and biocompatibility after 4 months of treatment.

Methods

Twenty patients were enrolled in this study. All patients were dialyzed with the ELISIO™-210H dialyzer during the entire study. After a one-month wash-out period all with HD, patients were randomly assigned to two treatment groups, "HD" (n=10) and "HDF" (n=10) for a four-month period. After the wash-out period, dialysis conditions remained unchanged for each patient (3 sessions/week for 4 months; 3 to 4 hours/session; with a blood flow QB=300-400mL/min, ultrapure bicarbonate buffered dialysate, dialysate flow QD=500-700mL/min, ultrafiltrate flow QF=110-120mL/min [adjusted to weight loss], substitution flow QF=100mL/min [post-dilution]). At time points M0, M1, M2, M3 and M4 (after 0, 1, 2, 3 and 4 months of treatment respectively), removal rates (urea, creatinine and beta2-microglobulin [β_2m]), instant clearances of urea and creatinine after 60 min of dialysis, dialysis dose and dialysate losses of albumin were measured. At M0 (= randomization) the removal of inflammatory, oxidative stress, coagulation and apoptosis markers was determined. At M4 (4 months of treatment after randomization) the evolution of inflammatory, nutritional, oxidative stress, coagulation, apoptosis, cell activation and bone disease markers were observed. The comparisons between the HD and HDF groups were performed using Mann-Whitney non parametric tests. Friedman and sign tests were used to compare variables over the time within each group.

Results

The ELISIO™-210H dialyzer was well tolerated by all patients, both in HD and HDF during the entire study period (5 months including the wash-out period). The urea Kt/V demonstrated a tendency to increase between M0 and M4, in both HD and HDF (Fig. 1). Albumin losses into the dialysate were higher in HDF than in HD, but most of the values were below 1.0 g/session in HDF and below 0.5 g/session in HD (Fig. 2). A significant increase in β_2m reduction rate was observed in the HDF compared to the HD group at M1, M3 and M4 (Fig. 3). A significant decrease in Time Average Concentration of β_2m was observed in HDF compared to HD at M1, M2, M3 and M4 (Fig. 4).

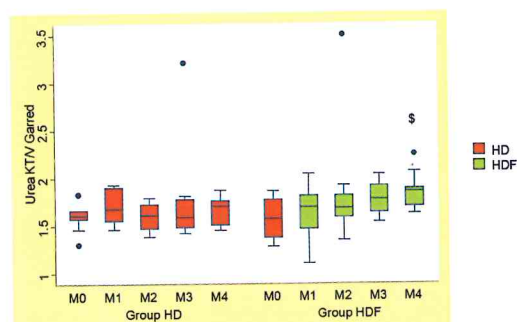


Figure 1: Dialysis dose urea Kt/V (Garred); ELISIO-210H in HD vs HDF
(* p < 0.05 vs M0)

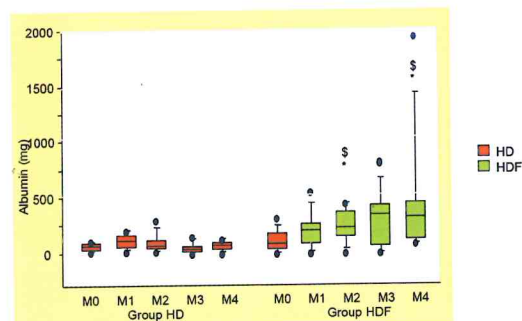


Figure 2: Albumin losses into the dialysate with ELISIO-210H in HD vs HDF
(* p < 0.05 vs HD; \$ p < 0.05 vs M0)

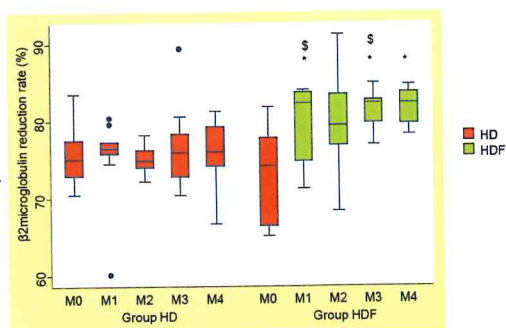
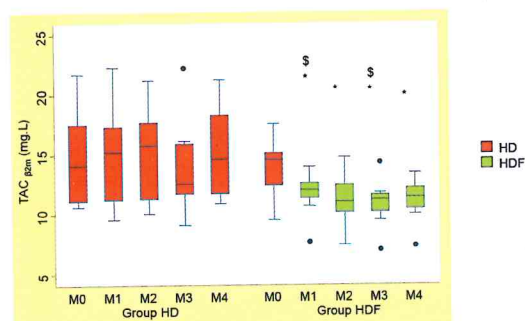


Figure 3: beta2-microglobulin reduction rate; ELISIO-210H in HD vs HDF
(* p < 0.05 vs HD; \$ p < 0.05 vs M0)



TAC β_2m (Time Average Concentration) = logarithmic mean of pre- and post-dialysis β_2m
Figure 4: TAC of beta2-microglobulin; ELISIO-210H in HD vs HDF
(* p < 0.05 vs HD; \$ p < 0.05 vs M0)

Regarding biocompatibility parameters, no significant difference was observed between both techniques particularly in terms of inflammation. Indeed, CRP level did not change during the entire study between HD and HDF even though high efficiency (high volume) was performed in HDF (not shown).

Conclusion

The Nipro ELISIO™-210H dialyzer was safely used in all the patients included in this study. Use of this dialyzer was associated with an excellent removal of beta2-microglobulin whatever the technique used (HD or HDF) and an excellent biocompatibility profile was achieved with HDF technique.

Impact of Nanotechnologically Modified Dialyzer on Dialysis Removal Capacity

Introduction

The removal of low-molecular weight proteins (LMWPs) has become one of the targets of modern high efficacy dialysis strategies. A current trend in dialysis membrane engineering is to maximize the permeability for larger LMWPs while retaining albumin. In the present study, the Nipro ELISIO™-170H* dialyzer, equipped with a nanotechnologically modified second generation synthetic high-flux dialysis membrane named POLYNEPHRON™, and a first generation DIAPES®-HF800 membrane, both made from the same polyethersulfone polymer backbone, were applied to the same patients in a hemodialysis (HD), and an on-line pre-dilution hemodiafiltration (pre-HDF) and an on-line post-dilution hemodiafiltration (post-HDF) setting. The removal ratio of a broad range of uremic retention solutes was evaluated.

Methods

The study was performed with a prospective cross-over randomized open label design. Fourteen stable, CKD stage 5D patients (10M+4F, mean age 74.0 ± 8.4 years), who had been on thrice weekly maintenance dialysis for at least 6 months, were randomized for two dialyzers with the same surface area (1.7 m^2): PES-170DS (DIAPES®-HF800 with PET[Performance Enhanced Technology]) and ELISIO™-170H* (Polynephron™ with RIPPLE structure), both produced by Nipro Corp. (Osaka, Japan). Each patient received one week of three consecutive treatments with HD, pre-HDF and post-HDF with each of the two dialyzers. The order of dialyzer type but not that of the dialysis mode was randomized. Before the start of the study and before changing the dialyzer type a wash-out period of two weeks consisting of low-flux dialysis (FX 10, Fresenius Medical Care, Bad Homburg, Germany) was performed. Effective blood flow rate was set at 300 ml/min. Dialysate flow rate was set at 500 ml/min during HD sessions and at 800 ml/min during HDF sessions. Infusion flow rates of 75 ml/min (25% of Q_B) and 150 ml/min (50% of Q_B) were applied in post-HDF and pre-HDF respectively. Samples were collected during the third (mid week) session of each respective period. Removal ratio (RR, %) of small water-soluble compounds (urea and uric acid), LMWPs (β_2 -microglobulin, cystatin C, myoglobin and retinol-binding protein) and protein-bound solutes (hippuric acid, indole acetic acid, indoxylsulfate and p-cresylsulfate) was assessed, together with albumin losses into the dialysate. For statistical analysis a one-way ANOVA with correction for multiple comparisons was used.

Results

While comparing the two types of membranes, the second generation dialyzer resulted in a higher RR for urea, but only in the HD mode (Fig. 1), probably due to the superiority of the "RIPPLE" structure of the fibers over the "PET". For the LMWPs, there is a distinct superiority of the second generation membrane, which became more pronounced as MW increased. The second generation membrane nevertheless resulted in lower albumin losses but only during post-dilution hemodiafiltration. No differences in RR were detected for both the small water-soluble compounds and the protein-bound compounds. Comparing dialysis strategies, convection removed the same amount of solute or more as compared to diffusion.

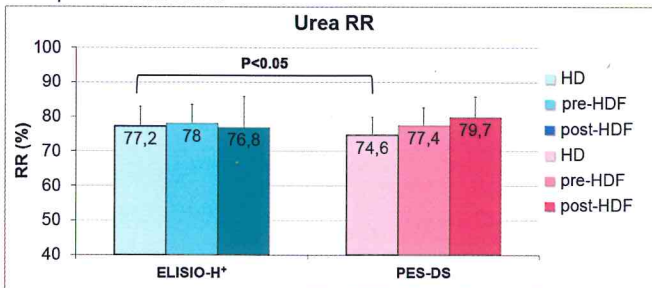


Figure 1: RR of urea was significantly higher with the ELISIO-170H* compared to the PES-170DS only in HD mode.

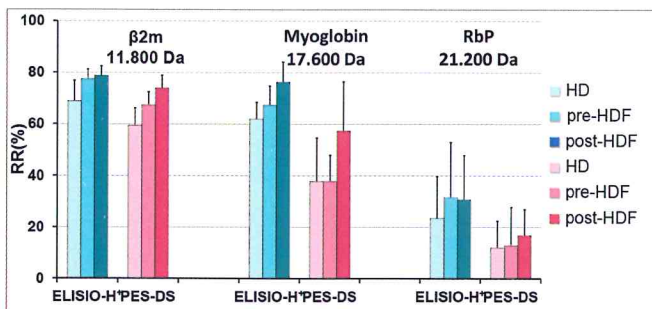


Figure 3: The RRs of β_2m and myoglobin were significantly higher with the ELISIO-170H* than with the PES-170DS, for all treatment modes. The superiority of the ELISIO becomes more pronounced with increasing MW.

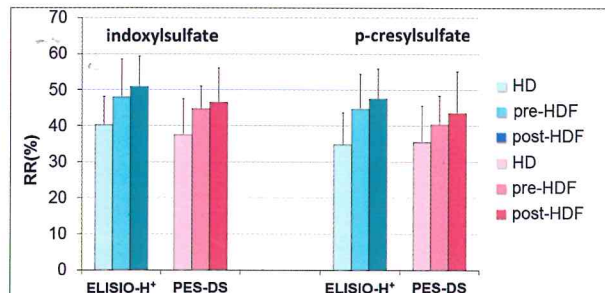


Figure 2: Removal of indoxylsulfate and p-cresylsulfate. There were no differences between the two membranes but the RR was higher in HDF compared to HD without difference among convective strategies.

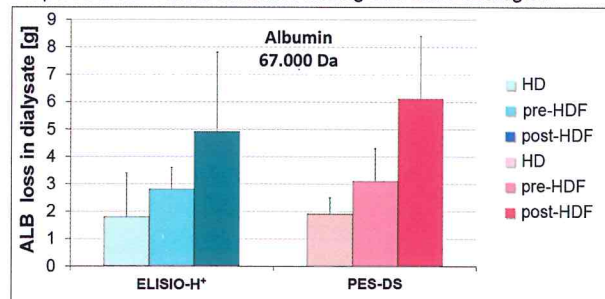


Figure 4: Albumin loss in the dialysate [g] per each of the different treatments. Lower albumin losses were observed with ELISIO-170H*, but only in post-HDF.

Conclusion

Second generation nanotechnologically manufactured large pore dialyzers have a superior removal capacity for the LMWPs; this effect grows as MW increases. In addition, convective strategies proved superior to HD, especially for most LMWPs and the protein-bound solutes with substantial protein binding. Differences between convective strategies (pre-dilution vs post-dilution) are more

prominent for the first generation dialyzers. The results demonstrate that the 2nd generation dialyzer (ELISIO-H*) has a sharper sieving profile than the PES-DS, as ELISIO-H* leaks the same or smaller amounts of albumin, but yields clearly higher LMWP removals in all treatment modes.

ELISIO™ POLYNEPHRON™:

Performance Parameters and Specifications

Performance		ELISIO™-H								ELISIO™-M					
Parameter	Qb/Qd (mL/min)	9H	11H	13H	15H	17H	19H	21H	25H	11M	13M	15M	17M	19M	21M
Effective Surface Area (m²)		0.9	1.1	1.3	1.5	1.7	1.9	2.1	2.5	1.1	1.3	1.5	1.7	1.9	2.1
KOA Urea (mL/min)*		778	916	1190	1351	1614	1771	1976	2269	801	902	1027	1145	1292	1450
Clearances (mL/min)**															
Urea	200/500	190	193	196	198	198	199	200	200	190	192	194	196	197	198
	300/500	246	257	272	278	285	288	291	294	248	256	264	270	276	281
	400/500	278	298	316	326	337	345	348	363	285	298	309	318	318	334
	400/800	307	327	347	359	368	373	378	386	311	326	339	350	360	369
	500/800	339	365	392	408	420	430	437	460	350	368	384	397	409	420
Creatinine	200/500	177	184	191	196	197	198	199	200	181	185	189	192	195	198
	300/500	218	233	250	259	268	273	275	285	226	236	244	251	257	263
	400/500	242	261	280	296	306	314	326	342	251	266	279	290	300	309
	400/800	275	297	318	333	349	358	363	377	277	295	309	323	334	345
	500/800	292	326	353	368	388	409	415	431	304	323	340	355	367	379
Phosphate	200/500	163	171	178	184	188	192	195	196	156	163	170	176	181	186
	300/500	200	213	230	241	254	258	265	276	183	198	211	221	231	240
	400/500	223	246	265	275	292	305	314	329	202	219	233	246	257	267
	400/800	242	263	291	305	322	335	339	352	220	241	258	274	287	300
	500/800	259	293	317	337	357	371	378	405	236	260	280	298	314	328
Vitamin B ₁₂	200/500	116	128	140	150	157	164	166	178	99	109	118	125	132	138
	300/500	134	148	165	180	190	200	206	224	111	123	134	143	151	158
	400/500	139	161	181	194	211	222	228	247	113	128	140	151	161	170
	400/800	151	173	197	215	231	245	254	273	120	138	153	167	179	189
	500/800	159	183	209	231	248	263	270	296	132	149	163	176	188	198
Inulin	200/500	81	86	96	102	110	119	124	153						
	300/500	89	94	102	112	121	132	145	171						
	400/500	92	96	109	118	129	139	151	182						
	400/800	97	97	113	125	132	149	159	195						
	500/800	101	102	117	131	140	156	166	210						
Myoglobin	200/500	58	63	74	84	91	101	104	116						
	300/500	61	68	80	90	98	107	111	126						
	400/500	63	76	84	94	107	113	122	137						
	400/800	68	78	88	99	111	116	125	139						
	500/800	70	87	99	110	123	131	138	145						
KUF (mL/hr/mmHg)***		53	59	64	67	74	76	82	93	15	17	20	22	25	27
Sieving Coefficient****	Vitamin B ₁₂	0.99													
	Inulin	0.93													
	Myoglobin	0.22													
	Albumin	<0.01													

Item Name	Description
DD+ELISIO-C-09H	ELISIO-09H PP (0.9 m²) Synthetic Hemodialyzer
DD+ELISIO-C-11H	ELISIO-11H PP (1.1 m²) Synthetic Hemodialyzer
DD+ELISIO-C-13H	ELISIO-13H PP (1.3 m²) Synthetic Hemodialyzer
DD+ELISIO-C-15H	ELISIO-15H PP (1.5 m²) Synthetic Hemodialyzer
DD+ELISIO-C-17H	ELISIO-17H PP (1.7 m²) Synthetic Hemodialyzer
DD+ELISIO-C-19H	ELISIO-19H PP (1.9 m²) Synthetic Hemodialyzer
DD+ELISIO-C-21H	ELISIO-21H PP (2.1 m²) Synthetic Hemodialyzer
DD+ELISIO-C-25H	ELISIO-25H PP (2.5 m²) Synthetic Hemodialyzer
DD+ELISIO-C-11M	ELISIO-11M PP (1.1 m²) Synthetic Hemodialyzer
DD+ELISIO-C-13M	ELISIO-13M PP (1.3 m²) Synthetic Hemodialyzer
DD+ELISIO-C-15M	ELISIO-15M PP (1.5 m²) Synthetic Hemodialyzer
DD+ELISIO-C-17M	ELISIO-17M PP (1.7 m²) Synthetic Hemodialyzer
DD+ELISIO-C-19M	ELISIO-19M PP (1.9 m²) Synthetic Hemodialyzer
DD+ELISIO-C-21M	ELISIO-21M PP (2.1 m²) Synthetic Hemodialyzer

* ELISIO™-H: Qb 300mL/min, Qd 500mL/min, Qf 10mL/min
 ELISIO™-M: Qb 300mL/min, Qd 500mL/min, Qf 10mL/min

** In Vitro Test Condition (EN1283): Qf 10mL/min.

*** KUF (EN1283): Bovine Blood (Hct 32±2%, Protein 60g/L, 37°C), Qb 300mL/min.

**** SC (EN1283): Qb 300mL/min, Qf 60mL/min.



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