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# Importance of Development of Dialysis Membranes for Purification of Small, Middle, High Molecular Weight and Protein-Bound Uremic Toxins: The Asymmetric Cellulose Triacetate (SOLACEA ™- H)

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## Abstract

**Introduction:** New cellulose Asymmetric Triacetate membranes improve the filtration properties and blood compatibility because of the asymmetric structure and smooth surface. The aim of our study was to evaluate the purifying efficacy of the new dialyzer, Solacea™-H (Nipro Corporation - Japan), as regards low molecular weight (LMW), medium molecular weight (MMW), high molecular weight (HMW) toxins and PBUT during on-line hemodiafiltration treatments.

**Materials and Methods:** Eight stable HD patients on three-weekly dialysis schedule, were evaluated after switching to the Solacea dialyzer (2,1$m^2$ surface area), during 6 on-line haemodiafiltration sessions. In every patient, blood tests were performed during the first 3 dialysis sessions and on the first and third dialysis session of the second week. The purification of the main standard parameters (LMW toxins), the removal of MMW toxins such as β-2 microglobulin, HMW toxins such as myoglobin and PBUT solutes such as total indoxylsulphate (TIXS) and p-cresol (T PCS), bound for 90% to serum albumin, and their free fractions, that represent less than the 10% of their total concentrations, were evaluated during on-line HDF treatments. The statistical differences, before and after dialysis, were calculated with the student's t-test for paired data.

**Results:** At the end of each haemodiafiltration sessions there was a significant decrease of the LMW toxins with a consistent Kt/V (1,4) and a high urea removal rate (69,3%). The concentrations of MMW and HMW toxins decrease by 50-70%. As regards the PBUT removal, total PCS and IXS decreased by 27-33%, while free fractions were reduced of 55-65%. However the values of both total and free fractions of PCS and IXS returned to similar values at the start of each subsequent dialysis. No side effects from intolerance to treatment were registered.

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**Conclusions:** In conclusion our experience with the Solacea dialyzer seems to demonstrate a remarkable purifying efficacy against small, medium and high-sized molecules as well as PBUT (pcresilsulphate and indoxylsulphate) that, even if removed for more than 30%, on the next sessions return to the previous dialysis high values.

**Keywords:** ATA membranes; Hemodialysis; Haemodiafiltration sessions; Solacea; Purification

**Abbrevations:** LMW: Low Molecular Weight; MMW: Medium Molecular Weight; HMW: High Molecular Weight; PBUT: Protein-Bound Uremic Toxins; HD: Hemodialysis; T IXS: Total Indoxylsulphate; TPCS: P-Cresol; eGFR: Estimated Glomerular Filtration Rate

## Introduction

Hemodialysis membranes made from cellulose triacetate have a good biocompatibility and have been used since the'80s.The asymmetric cellulose triacetate(the ATA™ membranes) is the evolution of this membrane that has been modified to achieve results, in terms of biocompatibility and removal properties, comparable to the most sophisticated and advanced synthetic dialysis membranes available on the market. The hydroxyl groups of cellulose membranes, in substitution of acetyl groups present in synthetic membranes, have been associated with the minor activation of the complement when the patient's blood comes into contact with the membrane and, therefore, it may be one of the causes of the absence of hypersensitivity reactions that on the contrary, have been reported with synthetic membranes. Therefore ATA membranes are hydrophilic membranes and unlike synthetic membranes, do not contain hydrophiliating elements, which are another possible cause of hypersensitivity reactions [1-4].

In terms of the removal efficiency newly developed ATA membranes substantially improve the filtration properties because of the asymmetric structure and smooth surface that enhance an improved dialysate flow distribution, so, preventing contact or excess packing among fibers and thus allowing better matching of blood and dialysate flows across all sections of the fiber bundle [1-4]. These characteristics associated with more effective solute clearance and pore size larger than conventional hemodialysis (HD) membranes promote the removal of protein-bound uremic toxins (PBUT), and low/middle to large molecular-weight solutes, including β2-microglobulin. In addition these membranes having a high cut-off molecular weight, allow a greater removal capacity than conventional HD membranes. The pores size allow slight losses of albumin: 1 g/session with a blood flow rate of 250 ml/min and a dialysate flow rate of 600 ml/min during 4h haemodiafiltration treatments with 12 liters of convective volume exchange, characteristics that approximate the behavior of glomerular filtration of toxins of the human kidney [4-5]. Another topic that in future will need to be addressed and currently little studied is highly polluting waste related to dialysis. At this regard the semi-natural fibers , like cellulose acetate, are manufactured from purified natural cellulose that derives primarily from two sources, cotton linters and wood pulp, that have less impact on waste management, reduced environmental impact and less pollution because the combination of both photo and biodegradation processes allow a synergy that enhances the overall degradation rate [6-7]. This latter aspect could help to significantly reduce the operating costs for highly polluting waste disposal; however this particular topic will need ad-hoc studies.

The aim of our study was to evaluate the purifying efficacy of this new dialyzer, Solacea™ - H (Nipro Corporation- Japan), as regards low molecular weight (LMW), medium molecular weight (MMW), high molecular weight (HMW) toxins and PBUT during on-line hemodiafiltration treatments. The haemodiafiltration exploits the high convection and diffusion within dialysis, and thus the purification capacity of this newly developed membrane, which in its earlier versions (symmetric cellulose triacetate) was not able to allow.

## Materials and Methods

Eight stable HD patients (Table.1) on three-weekly dialysis schedule, were evaluated after switching to the Solacea dialyzer (dialysis surface area of 2,1 $m^2$,UF coefficient of 76 ml/h/mmHg),during 6 on-line haemodiafiltration sessions (Qb≥ 250 ml/min , volume exchanged 21lt/session of post-dilution substitution fluid) each. All of them were dialysed through a proximal arteriovenous fistula. In every patient, blood tests were performed 5 times, pre and post dialysis, during the first 3dialysis sessions and on the first and third dialysis session of the second week, to evaluate besides the purification of the main standard parameters (LMW toxins), also the removal of MMW toxins such as β-2 microglobulin, HMW toxins such as myoglobin and PBUT solutes such as total indoxylsulphate (T IXS) and p-cresol (T PCS), bound for 90% to serum albumin, and their free fractions, that represent less than the 10% of their total concentrations. For total and free PCS and IXS fractions, respectively, 25µL of serum or 25µL of ultra filtrated serum (cut-off 30kDa) were mixed with 100µL of a solution of Metaphosphoric acid 5% and internal standard (PCS-D4). After centrifugation, 10µL of supernatant were diluted to 1mL with mobile phase. Samples were then analysed using an AB SCIEX TripleQuad™6500LC-MS/MS system [8]. The statistical differences were calculated with the Student's t-test for paired data, considering all the data collected, at the start and at the end of 5 dialysis sessions.

| Sex | Primary kidney Disease | Age | Hd vintage | Dry weight | Weight gain | QB | Previous treatment |
|---|---|---|---|---|---|---|---|
| | | years | months | Kg | Kg | ml/min | |
| M | g.sclerosis | 78 | 216 | 79,6 | 3 | 300 | HDF |
| M | diabetes | 52 | 216 | 102 | 4 | 350 | HDF |
| M | g.nephritis | 68 | 24 | 82,6 | 3,5 | 250 | HDF |
| M | g.sclerosis | 74 | 72 | 64 | 3 | 300 | HDF |
| F | g.nephritis | 52 | 48 | 66,5 | 3 | 300 | HDF |
| F | g.nephritis | 45 | 228 | 61,5 | 3 | 300 | HDF |
| M | diabetes | 65 | 132 | 94 | 4 | 330 | HDF |
| M | diabetes | 77 | 72 | 109 | 4 | 320 | BIC |
| mean | | 63,8 | 126 | 82,4 | 3,4 | 306 | |
| sd | | 12,7 | 83,6 | 17,9 | 0,5 | 29 | |

Table 1: Characteristics of 8 pts.
HDF = HEMODIAFILTRATION (high flux polysulphone 2,5 $m^2$) BIC = BICARBONATE HEMODIALYSIS (low flux polysulphone 2,1 $m^2$)

## Results

At the end of the haemodiafiltration sessions (Qb=300 ml/min), there was a significant decrease of the LMW toxins with a consistent Kt/V (mean value of 1,4 according to Daugirdas formula) not very different from the precedent KT/V mean values during polysulphone use (1,38±0,18). In addition we underline a high urea removal rate (69,3%); the concentrations of MMW and HMW toxins were reduced by about 50-70% (Table 2). As regards PBUT removal, total PCS and IXS decreased by 27-33%, while free fractions were reduced of 55-65 % (Table 3). Although significantly reduced at the end of each dialysis session, we observed that the values of both total and free fractions returned to similar values at the start of each subsequent dialysis, without any effect associated with short or long period between a dialysis session and the other (Figure 1-4).No patients had side effects from intolerance to treatment: hypotensive episodes or other complications like clots or filter circuit. All dialysis sessions were then completed in the prearranged time of 4 hours.

| Parameter | Pre-dialysis value | Post-dialysis value | Variation pre-post (%) |
|---|---|---|---|
| Urea (mg/dl) | 137,2 ± 26,8 | 42,2 ± 12,2 | 69,3 |
| Creatinine (mg/dl) | 11,0 ± 1,3 | 4,5 ± 1,0 | 58,6 |
| Phosphates (mg/dl) | 4,4 ± 1,1 | 2,1 ± 0,4 | 51,5 |
| β-2-microglobulin (mg/dl) | 32,3 ± 7,3 | 11,1 ± 4,2 | 65,8 |
| Myoglobin (mg/dl) | 216,3 ± 100,0 | 76,9 ± 31,4 | 64,5 |
| Albumin (g/dl) | 3,6 ± 0,3 | 4,2 ± 0,4 | 14,3 |
| Total Protein (g/dl) | 6,4 ± 0,5 | 7,4 ± 0,7 | 13,5 |
| Hemoglobin (g/dl) | 11,4 ± 1,0 | 13,0 ± 1,5 | 12,3 |
| Dialysis dose (Kt/V) | 1,4 ± 0,3 | | |

Table 2: Pre-dialysis vs. post dialysis (mean ± s.d.) and removal rate values of urea, creatinine, phosphates, Beta2 -microglobulin and myoglobin on HDF treatments with the Solacea 21H dialyzers.

| Parameter | Pre-dialysis (µM/l) | Post-dialysis (µM/l) | p | Removal rate (%) |
|---|---|---|---|---|
| Total IXS (n=8) | 333,7 ± 127,2 | 224,1 ± 80,5 | < 0,001 | 32,9 |
| Total PCS (n=7) | 412,1 ± 157,1 | 299,0 ± 98,7 | < 0,001 | 27,2 |
| Free IXS (n=8) | 42,2 ± 23,9 | 17,8 ± 11,0 | <0,001 | 57,9 |
| Free PCS (n=7) | 48,0 ± 43,4 | 16,8 ± 8,1 | < 0,001 | 64,9 |

Table 3: Pre-dialysis, post-dialysis serum levels (mean ± s.d.) and removal rate (%) of Protein -bounded and free P-cresil sulfate and indoxyl sulfate during HDF treatments (Qb=300 ml/min, Total convective volume = 21 l/session) with the Solacea 21H dialyzers.

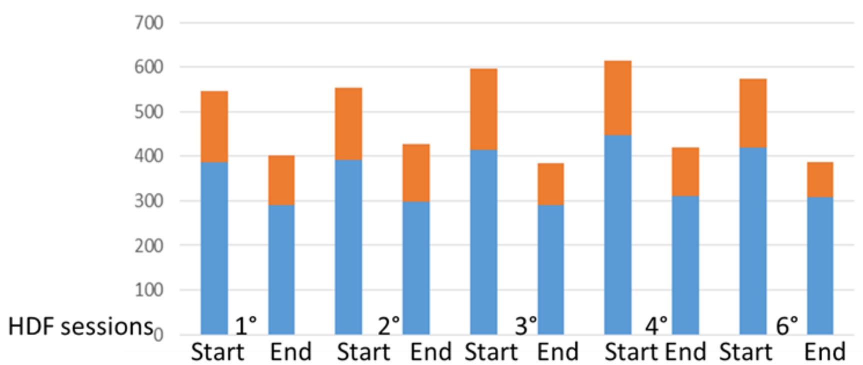


Figure 1: Total P Cresol behavior during 5 HDF sessions ± SD µMol /l.

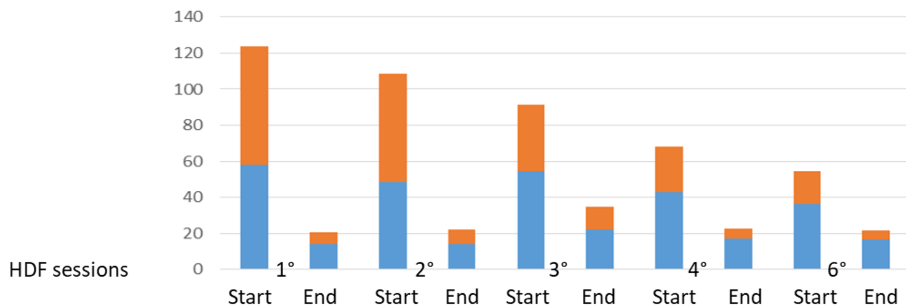


Figure 2: Free P Cresol behavior during 5 HDF sessions ± SD µMol /l.

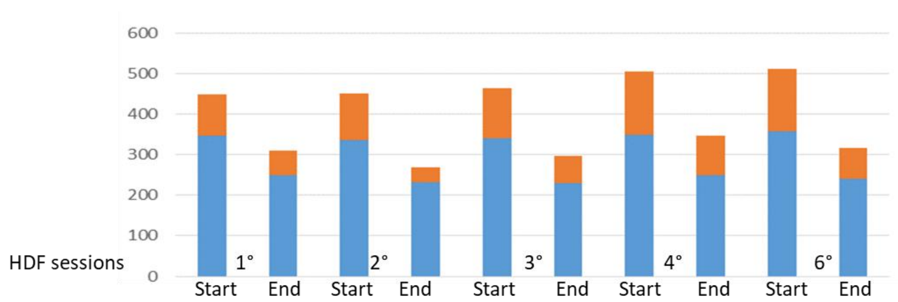


Figure 3: Total Indoxylsulphate behavior during 5 HDF sessions ± SD µMol /l.

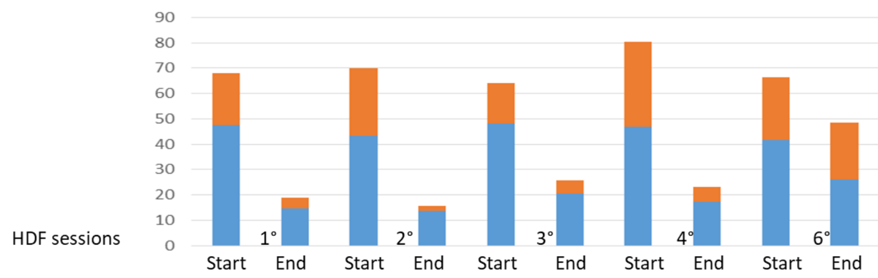


Figure 4: Free Indoxylsulphate behavior during 5 HDF sessions ± SD μMol /l.

## Discussion

Our data confirm the previous works by other authors of the efficacy of asymmetric cellulose triacetate with respect to small and medium-sized molecules associated with significant removal of PBUT, which cannot be achieved with conventional hemodialysis membranes, both in their protein bound and in their free fractions [1-6]. The removal mechanism of PBUT, which takes into account for a number of factors such as membrane water permeability and convective effect [6], is primarily facilitated by adsorption on cellulose membrane of a single layer of human serum proteins that are stratified since the first minutes of the beginning of the dialysis session. Such a protein single layer facilitates the release of toxins bound to albumin and their passage, by both electric attraction and concentration gradient, through the membrane into the dialysate. Against these latest data, however, we stress our experience, monitoring the behaviour of sulfate metabolites concentrations during 5 HDF sessions that their reduction - higher than 30-50% - doesn't seem to last over time, because after 48 hours, PCS and IXS concentrations are back to the pre dialysis levels. This evidence suggests that the removal of sulfates metabolites, according to the results of the present study, could be used as useful markers of purifying efficacy, other than markers of clinical efficacy on cardiovascular disease, as reported by some authors. Therefore, our data seem to confirm what has already been reported by Wu and other authors [8-10], that IXS and PCS significantly increase with decreasing renal function and they can be regarded as valid markers for the progression of CKD and estimated glomerular filtration rate (eGFR). This illustrates one of the fundamental problems we have to face during uremia studies: the uremic retention solutes move in the same direction and when the glomerular filtration rate decades most likely a number of unknown solutes increase [8-11].

Our data seem to confirm this theory, so we agree that, from a statistical point of view, IXS and PCS can be considered mostly markers of renal function as well as to have systemic toxic effects. It is known that one of the limiting factors of dialyzers, especially during on-line HDF, is the loss of albumin. In the recent analysis conducted by Potier et al., among 8 of 19 membranes used on on-line HDF, it is stated that some of them have a greater albumin loss than recommended, and, therefore, that they should not be used in techniques with elevated convective transport [12]. Our study confirms the low albumin loss of the ATA dialyzers as confirmed by the increased post-dialysis level of about 15% with respect to the pre-dialysis ones. In fact the post dialysis albumin mean value , after being adjusted for the percentage increase in serum hemoglobin , does not show notable changes, confirming data from other authors who report, for this membrane, leakage of albumin around 1 gram unlike other membranes that during HDF lead to a loss of more than 6 grams per session [13]. This fact, together with its improvement in terms of mid-sized molecule clearance and its biocompatibility profile, would allow them to be used for on-line HDF [2-5].

## Conclusion

In conclusion, our experience with the Solacea dialyzer (asymmetric cellulose triacetate membrane) seems to demonstrate a remarkable purifying efficacy against small, medium and high-sized molecules as well as PBUT (pcresilsulphate and indoxyl sulphate). These latter even if removed for more than 30%, on the next dialysis sessions return to the previous dialysis high values. In addition, we must remember the lower polluting effect of cellulose derivatives materials with respect to more polluting synthetic membranes, a problem still not addressed, in the context of dialysis, but which over time will become vital for the well-being of the planet.

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