Luncheon Seminar

Contributions and Life Prognosis Made by Super High-Flux Dialyzers

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Chairman
Ikuto Masakane
Seieikai Medical Corporation

Contributions Made by Super High-Flux Dialyzers Based on Biocompatibility and Prognosis

Speaker
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Effects on Dialysis Patients According to the Choice of Dialysis Membrane and BPA

Speaker
Gonzalez-Parra Emilio
Universidad Autonoma de Madrid

The 63rd Annual Meeting of the Japanese Society for Dialysis Therapy
**Contributions Made by Super High-Flux Dialyzers Based on Biocompatibility and Prognosis**

**Speaker**
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**Table 1: Definition of ‘Super high-flux’**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low-flux</th>
<th>Mid-flux</th>
<th>High-flux</th>
<th>Super-flux</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>&lt; 200</td>
<td>200-220</td>
<td>220-228</td>
<td>&gt; 228</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>&lt; 1500</td>
<td>1500-1800</td>
<td>1800-2000</td>
<td>&gt; 2000</td>
</tr>
<tr>
<td>β2-MG</td>
<td>&lt; 5.2</td>
<td>5.2-12.4</td>
<td>12.4-14.6</td>
<td>&gt; 14.6</td>
</tr>
<tr>
<td>albumin permeability (kD)</td>
<td>&gt; 800</td>
<td>800-830</td>
<td>830-880</td>
<td>&gt; 880</td>
</tr>
</tbody>
</table>

**Table 2: Comparison of dialyzer membranes**

- PS: Polysulfone
- PES: Polyethersulfone
- PMMA: Polymethylmethacrylate
- Pokran: Polysulfone
- EPR: Polyetheretherketone
- PVP: Polyvinylpyrrolidone
- BPA: Bisphenol A

**Guidelines recommend HPM dialyzers**

JSST’s “Guidelines for Maintenance Hemodialysis: Hemodialysis Prescriptions” recommend the use of high-performance membrane (HPM) dialyzers. In 2005, HPM dialyzers were defined by a β2-MG concentration of at least 10 mL/min. In 2013, the albu

**PES and PMMA membranes are associated with good prognosis**

In JSST’s nationwide surveys in 2008 and 2010 on the type of dialyzers being used in Japan, the prognosis of patients treated with type V dialyzers was reported to be excellent in 2008. Although the number of patients differed for the various types of dialyzer membrane materials used, survival rate was significantly higher in patients treated with the PES or PMMA membrane than in those treated with the PS membrane. In 2010,
the survival rate was compared between seven types of dialyzers used in approximately 136,000 cases. Hemodialysis was performed with the PS membrane in over half of the patients (57.0%), followed by PES in 15.1%, cellulose triacetate (CTA) in 7.9%, polyethylenimine (PMMA) in 6.4%, polyethylene (PEPA) in 5.1%, polyacrylonitrile (PAN) in 1.9%, and ethylene-vinyl alcohol copolymer (EVOH) in 0.9%. Many of the patients’ background characteristics differed significantly among the types of dialyzer membrane materials used (Table 2).7 For example, more younger patients and more male patients were dialyzed using the PES membrane. Higher percentages of older patients and women were dialyzed using the EVOH membrane. The proportion of diabetic patients was high among patients dialyzed using the PAN membrane. After adjusting for basic factors such as age, sex, and duration of dialysis, prognosis turned out to be significantly better with the PES membrane than with the PS membrane. Further analysis was performed after adjusting for dialysis dose (Kt/V) and C-reactive protein (CRP) in normalized protein catabolic rate, creatinine generation rate, and C-reactive protein (CRP) in addition to basic factors. The hazard ratio was slightly decreased with the EVOH or PAN membrane, but the PES membrane was not affected by dialysis dose. Finally, after adjusting for nutrition- and inflammation-related factors such as serum albumin, normalized protein catabolic rate, creatinine generation rate, and C-reactive protein (CRP) in addition to basic factors and dialysis dose, the hazard ratios of the PES group persisted (Figure 4).6 Additionally, after propensity score matching, the PES and PMMA membranes were associated with a better prognosis than the PS membrane (Figure 5).6 The effect of BPA is also implied, given that the EVOH and PMMA membranes do not contain BPA.

**Table 2.** Demographic, clinical, and laboratory values in hemodialysis patients according to types of dialyzer membranes

<table>
<thead>
<tr>
<th>Type</th>
<th>N (%)</th>
<th>Age (Years)</th>
<th>Sex (% woman)</th>
<th>Dialysis history (year)</th>
<th>BP history (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTA</td>
<td>1000</td>
<td>75.1 ± 10.6</td>
<td>56.3</td>
<td>5.9</td>
<td>40.1</td>
</tr>
<tr>
<td>EVOH</td>
<td>250</td>
<td>70.0 ± 11.6</td>
<td>45.7</td>
<td>6.8</td>
<td>33.0</td>
</tr>
<tr>
<td>PEPA</td>
<td>200</td>
<td>69.2 ± 11.9</td>
<td>41.6</td>
<td>7.4</td>
<td>31.3</td>
</tr>
<tr>
<td>PMMA</td>
<td>500</td>
<td>68.1 ± 12.2</td>
<td>37.2</td>
<td>8.3</td>
<td>28.2</td>
</tr>
<tr>
<td>PAN</td>
<td>150</td>
<td>68.8 ± 12.1</td>
<td>41.6</td>
<td>7.7</td>
<td>28.6</td>
</tr>
<tr>
<td>PS</td>
<td>1000</td>
<td>78.0 ± 11.8</td>
<td>60.1</td>
<td>7.8</td>
<td>34.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4500</td>
<td>73.9 ± 10.9</td>
<td>53.1</td>
<td>7.2</td>
<td>32.5</td>
</tr>
</tbody>
</table>

**References**
2) Chronic maintenance dialysis in Japan as of December 31, 2009.
5) Bosch-Panadero E et al. JASN. 2015.

**Figure 4.** Hazard ratios of all-cause mortality among 7 types of dialyzer membranes using Cox proportional hazards regression

**Figure 5.** Hazard ratios of all-cause mortality after propensity score matching for 6 types of dialyzer groups compared to the PS group

**Conclusion**

Even though Japan does not use the term “super-high flux dialyzer” as is used internationally, more than half of dialysis patients in Japan are currently being treated using super-high flux dialyzers. With respect to the biocompatibility of super-high flux dialyzers, greater use of high-performance dialyzers should be recommended while, at the same time, the effects of PVP and BPA should be investigated. Also, further long-term prospective studies are needed to clarify these findings, including whether the PES and PMMA membranes can improve prognosis.

**Clarification of the effects of bisphenol A, the new uremic toxin, is urgently needed**

Bisphenol A (BPA) is an environmental hormone whose chemical structure is similar to that of pheno- lols, which are protein-bound uremic toxins. Even in very low concentrations, BPA is capable of altering cell function. Exposure to BPA has been associated with the development of obesity, insulin resistance, metabolic syndrome, diabetes, and atherosclerosis. BPA is a new uremic toxin whose mechanism of action needs to be urgently investigated (Figure 1). Used in a variety of materials such as polycarbonates and resin, more than two million tons of BPA are produced annually. The chemical is also used in the synthesis of polysulfones and polyether ketones, in addition to plastic bottles, toothpaste, and packaging materials, and as an antioxidant for plasticizers. Furthermore, we are exposed to BPA on a daily basis given that epoxy resins containing the chemical are used in almost all food and beverage cans.

The use of BPA in baby products has been restricted internationally. For example, in 2011, the European Chemicals Agency banned the use of plastic baby bottles containing BPA. And, in 2012, the U.S. Food and Drug Administration announced that it would prohibit the use of BPA in baby bottles and cups (Figure 1).

**Verification of BPA toxicity**

When taken orally, BPA is excreted in urine after absorption into the intestines and metabolism in the liver. When entering the body through a non-oral route, BPA is incorporated directly into the blood in its unconjugated form. As a result, it will not be metabolized and will not undergo glucu- ronidation to the water-soluble BPA glucuronide. The water-soluble form is easier to remove with dialysis. Given that BPA is used in many types of dialysis equipment, including dialyzers, I believed it was necessary to investigate whether BPA was toxic or not in order to improve the management of patients with kidney disease. So, we conducted a study of oral administration of high concentra- tions of BPA (20 μg/kg/day) in mice. The kidneys, testes, and bladder showed signs of BPA exposure leading to urethral obstruction. This indicates that the ingestion of BPA has adverse effects on the body.

**Choice of hemodialysis membrane affects serum BPA levels**

We conducted a clinical study on how the choice of hemodialysis membrane affects serum BPA.
levels. BPA concentration in the blood of 69 dialysis patients after treatment was compared after alternate use of the PS and PES membranes. First, through blood sampling before treatment, we found that dialysis patients had higher serum and intracellular BPA concentrations than healthy controls.

The patients were separated into two groups: 28 were dialyzed using the PS membrane and 41 using the PES membrane. Dialysis was continued for 3 months with one membrane, then followed by 3 months of treatment with the other membrane. The group that used the PS membrane saw an increase in BPA concentration (from 48.8±6.8 to 69.1±10.1 ng/mL) but a decrease after switching to the PES membrane (from 70.6±8.4 to 47.1±7.5 ng/mL). Conversely, the group that initially used the PES membrane saw a decrease in BPA concentration but an increase after switching to the PS membrane (Figure 2). The results suggest that BPA concentrations in blood can be lowered with the use of dialyzers with a BPA-free PS membrane.

Another study was also conducted for online hemodiafiltration (HDF). Although the significant decrease seen in BPA concentration after changing from the PS membrane to the PES membrane was the same as that seen in the hemodialysis study, the concentration did not change considerably after switching from the PES membrane to the PS membrane. The differences between the two membranes after 3 months of online usage were not observed in the HDF study. However, it is notable that BPA concentration was considerably increased among patients using the PS membrane after 6 months of usage (Figure 3).

**PS membranes increase oxidative stress**

Next, a study on oxidative stress markers according to the type of membrane used in dialyzers compared the expression levels of oxidative stress proteins in peripheral blood mononuclear cells collected from patients dialyzed with the PS and PES membranes. The expression levels of peroxiredoxin-1, transcription factor Nrf2, and heme oxygenase-1 (HO-1) were significantly higher with the PS membrane. The results were similar for oxidative stress proteins in peripheral blood mononuclear cells, with quinone oxidoreductase-1 and superoxide dismutase-1 as well as HO-1 and Nrf2 also increasing with the PS membrane. On the other hand, no significant changes were observed with the PES membrane (Figure 4).

Comprehensive research using inflammatory biomarkers in plasma for CRP and interleukin-6 (IL-6) was also conducted with the PS and PES membranes. Patients were dialyzed using the two types of membranes alternately for 3 months each, which resulted in increased levels of both CRP and IL-6 after dialysis with the PS membrane and decreased levels with the PES membrane. Inflammatory reactions were also observed after culturing peripheral blood mononuclear cells with different concentrations of BPA for 24 hours. Expression levels of tumor necrosis factor mRNA and IL-6 increased with increasing BPA concentrations, thereby accentuating the inflammatory reaction.

The PS and PES membranes were also compared. While the PS membrane containing BPA increased inflammatory reaction, no reaction was observed for the PES membrane.

**PES membranes with high biocompatibility**

Lastly, I would like to discuss the biocompatibility of the PES membrane. In a clinical study conducted in Spain by Dr. Patricia Martinez-Miguel and colleagues, the CD14+CD16+ count in dialysis patients who were previously dialyzed with the PA membrane and underwent 4 months of treatment with the PES membrane decreased compared with the count in dialysis patients who were dialyzed with the PS and PA membranes. This suggests a better profile regarding activation of the inflammatory response, and that the PES membrane has better biocompatibility or contributes to increased removal of medium-sized toxic molecules.

A clinical study conducted in Germany in 2010 comparatively evaluated NIFRO’s PES membrane and two reference filters. Using the PES membrane resulted in the smallest increase in thrombin-antithrombin-III complex during dialysis and demonstrated exceptionally effective elimination of β2-macroglobulin and myoglobin. Another study of the PES membrane, by Locatelli in 2009, compared the impact of two synthetic high-flux dialyzers on renal anemia. After 6 months of continual dialysis treatment using the respective membranes, the hemoglobin concentration of patients dialyzed with the PES membrane significantly increased. Furthermore, the erythropoietin dosage for patients dialyzed with the PS membrane increased but decreased for those dialyzed with the PES membrane. These results imply that anemia will improve if the PES membrane is used (Figure 6).

**Conclusion**

BPA is an endocrine disruptor with multiple biological effects that is metabolized in the liver and eliminated by the kidneys. It must be removed in patients with chronic kidney disease because its accumulation causes systemic effects. Like p-cresol, BPA causes an increase in inflammation and oxidative stress in dialysis patients. The European Commission’s Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) recommends avoiding BPA in materials used in dialysis. For these reasons, BPA is an exogenous uremic toxin to which exposure should be avoided in dialysis patients. There are a few membranes that do not contain BPA, such as the PES membrane. The need to reduce inflammation and oxidation has been shown in multiple studies, and BPA may be associated with these toxic effects.

**References**