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- Plasma TNF-α を測定

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Postdialysis Fatigue: Lack of Effect of a Biocompatible Membrane

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• Tumor necrosis factor-α (TNF-α) has been shown to have somnogenic properties. Plasma levels of this cytokine have been found to increase significantly during dialysis with a bioincompatible (cuprophane) membrane in patients with postdialysis fatigue (PDF). We conducted a crossover study with random assignment to ascertain whether a biocompatible membrane might attenuate the increase of TNF-α and severity of PDF. Sixteen patients on maintenance hemodialysis underwent dialysis with either cuprophane (n = 8) or polymethylmethacrylate (PMMA; n = 8) membranes for 1 week and then switched to the opposite membrane during the second week. Predialysis and postdialysis measurements of plasma TNF-α levels were performed during the first and last dialysis treatments of each week. A fatigue score was determined from the sum of duration of fatigue and sleep within 6 hours of the completion of dialysis. TNF-α levels increased by an average of 18.3% during dialysis with cuprophane membranes but only 2.4% with PMMA membranes (*P* = 0.04). Despite this, fatigue scores remained unaltered (~4 of 6). Hence, the biocompatible membrane, PMMA, failed to alleviate PDF. This suggests that dialytic stimulation of TNF-α plays no substantial role in the pathogenesis of PDF.

INDEX WORDS: Hemodialysis; fatigue.

POSTDIALYSIS FATIGUE (PDF) of varying severity routinely affects a substantial portion of the hemodialysis population.[1] It further impairs the quality of life for patients whose lives are already compromised by chronic illness. Moreover, PDF is sometimes offered as the reason for patients' reluctance to conform to their optimal dialysis prescriptions, particularly when they involve additional dialysis days.

The cause of this effect of hemodialysis has been incompletely addressed in the renal literature. It is well-known to anyone involved in the day-to-day management of dialysis patients that excessive ultrafiltration can result in the acute onset of dramatic symptoms, including profound weakness, lightheadedness, and muscle cramps. These effects are often associated with hypotension and resolve with the administration of fluid.

The cause and management of chronic and recurrent interdialytic fatigue are not as well defined. Rapid osmolar flux is generally believed, although not proven, to be the basis for the development of many intradialytic and interdialytic symptoms, including PDF.[2,3] Dinarello[4] has proposed that proinflammatory cytokines, eg, interleukin-1β and tumor necrosis factor-α (TNF-α), generated by the exposure of blood to certain hemodialysis membranes, may be involved in the pathogenesis of dialysis "washout." There is a plethora of evidence showing that these cytokines induce slow-wave sleep in various mammalian species.[5]

In a previous study performed on patients dialyzed on bioincompatible membranes, we showed statistically greater intradialytic increases in TNF-α levels in patients with PDF than in those without PDF.[6] This observation suggests, but does not verify, that TNF-α and perhaps related cytokines are involved in the induction of PDF. It has been shown that biocompatible membranes do not stimulate the release of TNF-α and other cytokines to the extent that bioincompatible membranes do.[7-10] If somnogenic cytokines are indeed responsible for the production of a feeling of exhaustion after dialysis, then use of a biocompatible membrane should alleviate this problem. Using two different types of membranes and TNF-α as a marker of their biocompatibility, we performed a prospective crossover study to evaluate the potential role for this particular type of blood-membrane interaction in the pathogenesis of PDF.

MATERIALS AND METHODS

Patient Selection

We identified 25 outpatients receiving maintenance hemodialysis treatments with cuprophane membranes during day-

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time shifts who were previously defined to have chronic recurrent PDF by a combination of questionnaire and log data.[6] Briefly, the patients were screened initially and retrospectively by using a fatigue index questionnaire (one third of the sum of the intensity, duration, and frequency of PDF each rated from 1 to 5). Those with an index greater than 4 were assigned to a PDF group, whereas those with an index less than 2 were assigned to a non-PDF group. We validated the assignment by having each patient prospectively record, over 1 week, all time intervals during which they felt fatigued as well as required bedrest or sleep. Whereas non-PDF patients experienced little or no fatigue after dialysis and did not record periods of rest or sleep after dialysis sessions, PDF patients all described severe fatigue and requirement of at least 2 hours of rest or sleep within 6 hours of dialysis treatments. Twenty-one of the patients affected by PDF agreed to participate in the current study.

Protocol

A crossover study was performed over a 2-week period. During the first week, half of the patients were randomly assigned to dialyze either on a 1.2-m^2 surface area cuprophane membrane (Capillary Flow Dialyzer; Baxter Healthcare Corp, Deerfield, IL) or on a 1.25-m^2 low-flux polymethylmethacrylate (PMMA) membrane, (Toray, Tokyo, Japan). During the second week, patients were switched to the opposite membranes. Patients were blinded with respect to the type of membrane used during all dialysis treatments throughout the study. Each patient was dialyzed thrice weekly on a Baxter SPS 550 machine (Baxter Healthcare Corp). Dialysate was delivered at 500 mL and had the following composition: sodium, 138 mEq/L; calcium, 3.5 mEq/L; magnesium, 1.3 mEq/L; and bicarbonate, 36 mEq/L. Ultrafiltration was performed at a constant rate with the patient's estimated dry weight as the ultrafiltration goal.

Blood samples were drawn pre- and postdialysis during the first and last treatments of each week for subsequent TNF-α analysis. Levels of PDF were determined by analysis of 6-hour logs of sleep and perception of fatigue recorded by patients after each of these dialysis treatments. At the completion of the study, the patients submitted their log sheets to one of the investigators.

Analytic Methods

Blood samples were centrifuged, separated into cryotubes, and frozen at −20°C within 60 minutes of blood sample collection for subsequent analysis. Assays for TNF-α were performed in duplicate by using commercially available enzyme-linked immunosorbent assay kits (Quantikine HS, R&D Systems, Minneapolis, MN).

Fatigue scores were calculated as the sum of the hours of sleep and the hours of fatigue experienced by patients for up to 6 hours after each dialysis treatment. Pearson correlation was used to determine the relationship between TNF-α levels and fatigue scores. Initial comparison of fatigue scores was assessed by the Wilcoxon signed-rank test. Comparison of TNF-α levels and fatigue scores between membranes was performed by using analysis of variance with repeated measures. The interaction of fatigue and TNF-α levels between membranes was also evaluated by using repeated measures analysis with interaction. Analyses were performed on a personal computer using CRUNCH 4 (Crunch Corp, Oakland, CA) and SAS 6.07 (SAS Institute Inc, Gary, NC). Data are presented as mean ± standard error of the mean.

RESULTS

Five patients were not included in the data analysis because they were individuals who destabilized medically ($n = 2$) or submitted incomplete log sheets ($n = 3$). The remaining 16 patients had a mean age of 61 ± 3 years and included 9 men and 7 women. Causes of renal failure included diabetes mellitus ($n = 7$), hypertension ($n = 3$), chronic glomerulonephritis ($n = 4$), polycystic kidney disease ($n = 1$), and analgesic abuse ($n = 1$). On questioning at the completion of the study, these patients denied knowledge of which type of dialyzer they had been treated with during either phase of the study.

There were no significant differences between membranes in the percent reductions (pre- to postdialysis) of osmolality (6.4 *v* 6.3), body weight (3.2 *v* 3.3), and systolic blood pressure (9.0 *v* 9.0). TNF-α results, expressed as percent change from baseline, and fatigue scores are shown in Fig 1. The baseline levels of TNF-α were between 10.4 and 11.9 pg/mL and increased by nearly 20% in patients when dialyzed with cuprophane membranes. Despite significant suppression of the intradialytic augmentation of TNF-α levels by dialysis with PMMA membranes ($P = 0.04$), fatigue scores remained high and essentially unaltered ($P = 0.50$). There was no statistically significant correlation between TNF-α level and fatigue score for either cuprophane or PMMA membranes ($r = 0.24$ and $r = 0.03$, respectively).

To minimize the possibility of carryover effects between dialyzers, we compared TNF-α and fatigue levels obtained from the final dialysis treatments of each week, ie, a week apart. The results of this analysis amplified the above findings with suppression of intradialytic augmentation of TNF-α achieving a P of 0.02 and fatigue scores remaining unchanged ($P = 0.64$).

DISCUSSION

The small sample of subjects available to us for this study dictated the short time frame for its execution; we were concerned about potential dropout of already small numbers of these chroni-