Abandoning Peracetic Acid-Based Dialyzer Reuse Is Associated with Improved Survival

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Summary

Background and objectives Higher mortality risk reported with reuse versus single use of dialyzers is potentially related to reuse reagents that modify membrane surface characteristics and the blood-membrane interface. A key mechanism may involve stimulation of an inflammatory response.

Design, setting, participants, & measurements In a prospective crossover design, laboratory markers and mortality from 23 hemodialysis facilities abandoning reuse with peracetic acid mixture were tracked. C-reactive protein (CRP), white blood cell (WBC) count, albumin, and prealbumin were measured for 2 consecutive months before abandoning reuse and subsequently within 3 and 6 months on single use. Survival models were utilized to compare the 6-month period before abandoning reuse (baseline) and the 6-month period on single use of dialyzers after a 3-month “washout period.”

Results Patients from baseline and single-use periods had a mean age of approximately 63 years; 44% were female, 54% were diabetic, 60% were white, and the mean vintage was approximately 3.2 years. The unadjusted hazard ratio for death was 0.70 and after case-mix adjustment was 0.74 for single use compared with reuse. Patients with CRP ≥ 5 mg/L during reuse (mean CRP = 26.6 mg/ml in April) declined on single use to 20.2 mg/L by August and 20.4 mg/L by November. WBC count declined slightly during single use, but nutritional markers were unchanged.

Conclusions Abandonment of peracetic-acid-based reuse was associated with improved survival and lower levels of inflammatory but not nutritional markers. Further study is needed to evaluate a potential link between dialyzer reuse, inflammation, and mortality.

Introduction

A narrow majority of outpatient dialysis facilities practice single use of dialyzers, although reprocessing of dialyzers (“reuse”) remains prevalent in nearly half of all facilities in the United States, affecting approximately 40% of hemodialysis patients. The primary motivation for providers to continue reusing dialyzers is economic (1,2). Consensus exists that dialyzer reuse can be performed safely when fully compliant with national standards (3,4). Several epidemiologic studies found no difference in mortality rates between patients dialyzed using new or reused dialyzers, but several large studies demonstrated improved survival associated with single use of dialyzers (5–8). The most recent of them was conducted within Fresenius Medical Care–North America (FMCNA) after its decision to forego the reuse procedures that utilized predominantly formaldehyde and bleach: The results demonstrated a modest approximately 7% case-mix adjusted survival advantage for 18,137 patients whose facilities converted to 100% single use after a 90-day lag (i.e., “washout period”), although sensitivity analyses indicated that the survival advantage remained significant with a 60- or 120-day lag period (8).

Another opportunity to prospectively evaluate this issue occurred when FMCNA acquired the Renal Care Group in 2006 and subsequently converted its facilities from dialyzer reuse (predominantly using a peracetic acid mixture) to single use. This population presented a much smaller facility and patient pool available for study, but we hypothesized that a trend toward improved survival could be detected after a 90-day washout period. In addition, we prospectively tested a hypothesis that withdrawal from exposure to reuse (i.e., from peracetic acid mixture modified dialyzer components and/or residual reagent) may be associated with resolution of an inflammatory state (if present) with accompanying improvement in nutritional markers.

Methods Summary

Study Population

In January 2007, we prospectively identified outpatient hemodialysis facilities that were scheduled to abandon reuse of dialyzers with peracetic acid reagent during the month of May 2007. Logistic and personnel issues caused delayed conversion to single use in many of them, such that only 12 facilities initiated single use of dialyzers in May, and only 23...
facilities by July 31, 2007. Adult (≥18 years of age) maintenance hemodialysis patients treated in these 23 outpatient facilities provided the study cohort that formed the basis of this report.

Specific Laboratory Markers of Inflammation and Nutrition

A waiver of requirement for informed consent from individual patients for testing C-reactive protein (CRP) and prealbumin levels on residual blood was granted, and the study was approved by the New England Institutional Review Board (Wellesley, MA). Baseline CRP and prealbumin were measured in residual blood from routine monthly blood draws received by the central laboratory (Spectra Laboratories, Rockleigh, NJ, and Fremont, CA) from these 23 facilities during the 2 months before scheduled conversion to single use (March and April, 2007). Similarly, CRP and prealbumin were re-measured in August (approximately 1 to 3 months postconversion) and again in November (approximately 4 to 6 months postconversion). Immunoturbidimetric assays on an Olympus 5400 series chemistry analyzer were used to measure CRP (lower limit of detection 5 mg/L) and prealbumin (lower limit of detection 3 mg/dL). The corresponding values for routine monthly laboratory measurements of albumin and white blood cell (WBC) count were obtained from Spectra data batch-loaded into the FMCNA Knowledge Center data warehouse.

Analysis to Evaluate Change in Specific Laboratory Indicators during Single Use

Specific analyses for these special markers of inflammation and nutrition were conducted at two levels: baseline patients (patients who were present from day 1 and throughout the follow-up period) and period-prevalent patients facility-wide (representing aggregate values from baseline and all newly admitted patients combined into a facility average). The average prealbumin, albumin, CRP, and WBC levels were reported preconversion (mean of March and April values) and postconversion (once during the August blood draw [within the first 3 months] and a second sampling in November [approximately 4 to 6 months on single use]). A stratified analysis was performed with emphasis on the patients with detectable CRP ≥ 5 mg/L in the month of April to assess the change from preconversion baseline (last months of reuse) to single use thereafter. To facilitate computation of mean values, CRP results below the detection limits of the assay were assigned a value of 2.5 mg/L (i.e., midpoint between 0 and 5 mg/L). A sensitivity analysis that excluded patients from four facilities that did not have Diasafe (Fresenius USA, Walnut Creek, CA) filters before study initiation was performed to minimize potential confounding from improving water purity during the study period.

Analysis to Evaluate Change in Mortality Risk

Using a single crossover design, period-prevalent mortality data were collected for the last 6 months of reuse and the subsequent 6 months of single use after a 3-month lag period (with the conversion month counted as lag-month 1). The 3-month lag period allowed for a washout phase that is consistent with prior experience (8). All patients who were present at the beginning of each 6-month period formed the baseline patient cohort preconversion (i.e., reuse) and postconversion to single use. Age, gender, race, diagnosis of diabetes, dialysis vintage, and access type were collected for each of these patients as of the first day of each study period. Laboratory measurements were also collected for albumin, WBC count, hemoglobin, phosphorus, and estimated Kt/V (eKt/V), which was calculated by urea kinetic modeling (9).

For the 6-month mortality analyses in the subset of patients active at the beginning of each period (i.e., “baseline patients only”), gross mortality rates and normalized mortality rates (per 100 patient years) were compared. Survival models utilizing proc lifereg in SAS version 9.2 (Cary, NC) were constructed unadjusted (single use compared with reuse) and with adjustment for case mix (age, gender, race, diabetes mellitus, dialysis vintage and vascular access type). These mortality analyses were repeated at a facility-wide level in which all period-prevalent patients were included (baseline patients plus all other patients who were admitted to the facility during each 6-month period of reuse and of single use).

Results

Facilities that converted from reuse with peracetic acid mixture to single use of dialyzers (n = 23) had similar initial populations (i.e., at the beginning of each 6-month exposure period), which is shown in Table 1. The observed gross mortality rate for patients present at baseline was 13.0% during the 6-month reuse period, compared with 8.7% during the single-use period (P = 0.009), which is shown in Figure 1. The corresponding normalized mortality rates are depicted in Figure 2. Significant declines in gross and normalized mortality rates upon abandonment of reuse were observed not only for patients who were present at baseline but for all period-prevalent patients facility-wide (i.e., includes patients admitted to the facility during the period). Survival models (Figure 3) utilizing the reuse period as reference (i.e., hazard ratio [HR] of 1.00) indicated an unadjusted mortality HR of 0.70 (P = 0.003) and a case-mix adjusted HR of 0.74 (P = 0.01) for single use comparing patients present at the beginning of each period. This difference in mortality risk was attenuated but remained significant when all period-prevalent patients were compared facility-wide, with an unadjusted HR of 0.75 (P = 0.008) and a case-mix adjusted HR of 0.79 (P = 0.03).
Levels of inflammatory markers dropped lower than baseline, as shown in Table 2. The WBC count exhibited a statistically significant decline between April and August that was sustained until November within baseline patients and all period-prevalent patients facility-wide. The CRP burden was slightly lower in baseline patients with mean values of 16.5 mg/L in March/April, decreasing to 11.5 mg/L in August, as shown in Figure 1. Normalized mortality rates observed during the 6-month periods of reuse (preconversion) versus single use of dialyzers (postconversion) with a 3-month washout period (or lag period) in between, as shown in Figure 2.
14.8 mg/L in August, and then at 15.8 mg/L by November. However, these differences did not attain statistical significance. In contrast, period-prevalent patients’ mean CRP declined significantly from March/April to August (17.1 mg/L versus 14.5 mg/L, \( P < 0.008 \)). The CRP burden remained low by November (15.9 mg/L), albeit no longer significantly different from baseline. In April, out of 1692 patients with CRP results, there were 660 patients (39%) with CRP \( \geq 5 \) mg/L. In this subgroup of “inflamed” patients, there was a significant decline in CRP (mean of 24.6 mg/L) by almost 5 mg/L in August (19.8 mg/L, \( P = 0.0005 \)) that was sustained up until November (20.8 mg/L, \( P = 0.02 \)), which is shown in Figure 4. Furthermore, a parallel change in WBC count was observed in these 660 patients from \( 8.3 \pm 2.6 \times 10^{3}/\text{mcL} \) to \( 7.9 \pm 2.6 \times 10^{3}/\text{mcL} \) in August (\( P = 0.0007 \)) and \( 8.0 \pm 2.8 \times 10^{3}/\text{mcL} \) by November (\( P = 0.009 \)). Of note, approximately 46% of patients with CRP \( \geq 5 \) mg/L had undetectable levels by November, whereas in contrast approximately 32% of patients with undetectable CRP levels in April had detectable CRP in November. Although we observed appreciable changes in inflammatory markers, there were minimal changes in nutritional markers (albumin and prealbumin) from preconversion (March/April) and after 4 to 6 months of single use by November, as seen in Table 3. Sensitivity analyses that limited participation to patients dialyzed in 19 facilities that had been using Diasafe water filters before and during the study period had similar results.

### Discussion

The study revealed a substantial improvement in mortality during the 6-month period with single use of dialyzers (after the 3-month washout phase) after abandoning dialyzer reuse with peracetic acid. The observed 20% to 25% drop in case-mix adjusted mortality risk was larger than anticipated from prior experience (8). One major difference between these two FMCNA studies is the type of reuse reagent used—formaldehyde with bleach in approximately 80% of facilities in the prior study versus 100% peracetic acid mixture in the study presented here. We note from other independent

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**Table 2. CRP and WBC count as key inflammatory parameters of interest measured before conversion (average of March and April results) and after initiating single use in the months of August (approximately 1 to 3 months postconversion) and November (approximately 4 to 6 months postconversion)**

<table>
<thead>
<tr>
<th>Blood Draws</th>
<th>Baseline Patients Onlya</th>
<th>Period-Prevalent Patientsb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRP (mg/L)</td>
<td>WBC Count (10^3/mcL)</td>
</tr>
<tr>
<td>March/April</td>
<td>16.5 ± 24.2</td>
<td>7.8 ± 2.6</td>
</tr>
<tr>
<td>August</td>
<td>14.8 ± 27.4</td>
<td>7.7 ± 2.5c</td>
</tr>
<tr>
<td>November</td>
<td>15.8 ± 29.4</td>
<td>7.7 ± 2.5d</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD.

aOnly patients who were present at baseline and survived for the entire follow-up period.
bPatients at baseline plus all other patients admitted to the facilities during the 6-month period contributing one or more laboratory results (represents the mean of facility averages).
c\( P = 0.01 \) and d\( P < 0.01 \) compared with March/April; otherwise not statistically significant.
studies that stratified risk associated with reuse by type of reuse reagents that peracetic acid mixtures were associated with relatively greater mortal risk (5,6) albeit not in all studies (10).

Potential mechanisms to explain improvement in outcomes from abandoning the reuse procedure have been hypothesized but not previously demonstrated. A decrease of exposure to bacterial contaminants in the water run through the dialyzer’s blood compartment during reprocessing (and not usually passed through the equivalent of a Diasafe filter beforehand) may be one general factor. More specifically, changes in membrane characteristics and blood-membrane interface may be responsible for the various documented changes in water and solute permeability observed upon repeated exposure to peracetic acid mixture (11-14). Moreover, the interaction between the dialyzer membrane and the reuse reagent may differ between peracetic acid and formaldehyde (15,16). To our knowledge, none of these observations have been related to outcome. We postulated that regardless of the mechanism (e.g., exposure to the reused membrane, residual reagents, altered permeability of the membrane to toxins, or some combination of the above), one potential common pathway to detect a link might be through an inflammatory reaction and the accompanying nutritional manifestations.

We observed a statistically significant decline in WBC count associated with a trend toward lower CRP burden. In the subset of 660 patients with detectable inflammation (CRP > 5 mg/L) immediately before abandonment of reuse, a significant and sustained decline of the mean CRP burden by almost 5 mg/L was observed up to 6 months after conversion to single use of dialyzers. Overall, the CRP burden within the facility was also lower after conversion to single use. Although unmeasured confounding factors influence CRP levels, we propose that the clinical significance of the observed reduction in CRP levels may be relevant to the changes in WBC count and possibly mortality. However, we were unable to detect statistically significant changes in nutritional parameters between cohorts, including prealbumin, known to be more responsive to recent changes in protein intake and metabolism.

The prospective single crossover design of this study is an established method with known strengths and limitations. Facilities involved in the intervention arm of
the study served as their own control. A key strength of this design is that it minimizes environmental, geographic, socioeconomic, and source population differences between cohorts. One limitation is that the intervention and control phases are consecutive and not parallel, potentially allowing confounding from intercurrent events. However, the improvement in survival was temporally associated with the conversion and our results were robust even after case-mix adjustment. Moreover, findings were consistent with prior observations that patients who do not reuse dialyzers have relatively better outcomes (5–8). Of note, no large study utilizing contemporary dialytic methods has ever indicated the opposite—that reuse is associated with better survival than single use (2). A second limitation of the study involved the use of a CRP assay that had a lower limit of detection set at ≥ 5 mg/L. A high-sensitivity assay may have been more reactive to stimulatory exposures associated with reuse or single use. However, we note that recent comparisons between standard and high-sensitivity CRP assays documented excellent agreement between them, especially when utilized to predict mortality (17,18).

In conclusion, these findings indicate improved survival associated with abandonment of reuse with peracetic acid within 23 facilities that were converted to single use of dialyzers as part of a systematic quality improvement effort. We also observed an accompanying reduction in inflammatory burden, especially for patients who had inflammation present before conversion to single use. In contrast, we were unable to detect major changes in the nutritional markers albumin and prealbumin. Further studies are needed to evaluate potential mechanisms that can explain the survival benefits observed with abandonment of reuse, including the potential role of inflammation. Continued reassessment of dialyzer best practice is necessary as more data become available to inform patients and clinicians in evaluating their treatment options.

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Disclosures

All authors are employees of FMCNA. FMCNA provides dialysis services and manufactures dialyzers and other dialysis products.

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