Dialyser reuse-associated mortality and hospitalization risk in incident Medicare haemodialysis patients, 1998–1999

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Abstract

Background. The reuse of haemodialysers has been practiced in the United States for >20 years. We investigated mortality and hospitalization risk according to various reuse practices, testing the hypothesis that outcomes are improved in patients treated with dialysers cleaned with bleach and sterilized with formaldehyde.

Methods. We studied 1998 and 1999 incident Medicare haemodialysis patients, with follow-up through December 31, 2000 (49,273 patients). Clinical conditions and dialysis therapy were characterized from Medicare claims data. Included were patients who could be linked to a dialysis provider. Demographic characteristics were obtained from the Centers for Medicare and Medicaid Services (CMS) Medical Evidence Report. Mortality information was obtained from the CMS ESRD Death Notification; hospitalization information, from Medicare in-patient claims files. Data on reuse practices were obtained from the annual survey of haemodialysis units conducted by the Centers for Disease Control and Prevention.

Results. Cox regression analyses found no significant differences in mortality or first-hospitalization risk for patients in dialysis units not using bleach as a cleaning agent. Outcomes for patients treated in units using glutaraldehyde did not vary according to use of bleach. In the analysis of first-hospitalization risk, there was no difference according to various germicide/bleach combinations. Overall, there was no significant difference in relative risk of death or in hospitalization risk among the reuse groups (including the no-reuse group).

Conclusions. For the 1998–1999 period, reuse practices were not associated with a survival advantage or disadvantage. Our findings may reflect the National Kidney Foundation’s 1997 introduction of clinical practice guidelines, the intent of which was to bring about increased consistency of care within the dialysis community in the United States.

Keywords: chronic kidney failure; morbidity; mortality; renal dialysis

Introduction

Reuse of haemodialysers has been a consistent practice in the United States for >20 years. In the last 10 years, the practice of reusing dialysers increased to ~81% of dialysis units, then declined slightly through the year 2000 to ~78% of dialysis units [1]. Peracetic acid mixture, formaldehyde and glutaraldehyde have been the predominant types of germicide used in reuse practices in the United States. In 1991, almost 50% of reuse units were using peracetic acid mixture; by the year 2000, 62% of reuse units were using peracetic acid mixture [1].

The continued practice of reuse in the United States has been controversial; its safety has been disputed by a number of investigators [2–5]. Recent data (through 1996) have shown that there is little difference in outcome for US patients treated with reused dialysers versus those treated with single-use dialysers, a finding that differs from findings of studies conducted in the late 1980s [2,4,5].

The membranes used in the United States have changed dramatically in the last 10 years, with synthetic high-flux dialysers (as opposed to cellulose-based dialysers) being used more and more commonly [1]. Some investigators have hypothesized that reuse of high-flux dialysers with certain germicides may be associated with reductions in large-molecular-weight clearances, which may affect patient outcomes [6–8]. However, reuse practices that include the cleaning of high-flux dialysers with bleach (vs peracetic acid but no bleach) appear to be associated with improved large-molecular-weight clearance [9].
An observational study found a lower risk of death in patients whose high-flux dialysers were cleaned with bleach, as compared with other cleaning practices [9]. This finding was obtained using data on prevalent patients in December 31, 1993, with follow-up into 1994. Because clinical practices changed significantly during the ensuing years and increased attention has been paid to the quality of dialysis, anaemia treatment and reuse practices, we investigated reuse-associated mortality and hospitalization risk in 1998 and 1999. These were the most recent years governed by clinical practice guidelines from the National Kidney Foundation [10] for which data were available. We also chose the years 1998 and 1999 because the Centers for Disease Control and Prevention (CDC) surveillance surveys of dialysis units included data on reuse practices, including bleach cleaning.

It has been hypothesized that outcomes are improved in patients treated with high-flux dialysers cleaned with bleach and sterilized with formaldehyde, as compared with outcomes when other reuse practices are followed. This hypothesis is based on the potential for retained large-molecular-weight clearances in high-flux dialysers processed with bleach and formaldehyde [9]. Our intent was to test this hypothesis and also to investigate whether bleach cleaning in combination with other germicides was associated with lower hospitalization risk and mortality in haemodialysis patients.

### Subjects and methods

#### Patient selection

We studied 1998 and 1999 incident Medicare haemodialysis patients who were alive on haemodialysis for the first 9 months of renal replacement therapy for end-stage renal disease (ESRD), with follow-up through December 31, 2000 (49 273 patients). Patients survived at least 90 days beyond the first ESRD service date and then survived an additional 6 months (entry period), for which time haematocrit levels, comorbid conditions, measures of disease severity and dialysis therapy [urea reduction ratio (URR)] were characterized from Medicare claims data. We included those patients who could be linked to a dialysis provider (in order to characterize reuse practices) and had four or more erythropoietin (EPO) claims (in order to calculate mean haematocrit level) during the 6 month entry period. Demographic characteristics were obtained from the Centers for Medicare and Medicaid Services (CMS) Medical Evidence Report (Form 2728), which records date of birth, gender, race, renal diagnosis and first ESRD service date. Mortality information was obtained from the CMS ESRD Death Notification (Form 2746); hospitalization information was obtained from Medicare in-patient claims files.

#### Comorbidity

Because comorbidity is associated with patient survival, as shown on page 158 of the USRDS 2002 Annual Data Report [1], our analysis included adjustments for comorbid conditions, including atherosclerotic heart disease, congestive heart failure, peripheral vascular disease, other cardiac disease (valvular disease, arrhythmia, need for pacemaker), cerebro-vascular accident/transient ischaemic attack, cancer (excluding skin malignancies), chronic obstructive pulmonary disease and gastrointestinal disease (including gallbladder disease, liver disease and gastrointestinal bleeding). These conditions were determined for the 6 month entry period using data from Medicare Part A and Part B claims and following previously described procedures [11–13].

#### Disease severity, haematocrit level and dialysis unit variables

Disease severity measures included the number of blood transfusions (from Medicare Part A claims) and hospital days during the entry period. Mean haematocrit level for the entry period was calculated from the haematocrit value reported on EPO claims (minimum, four claims). Mean EPO dose per month was computed from the claims data and used as a surrogate for chronic inflammation, since EPO resistance is correlated with increased levels of interleukin-6 and C-reactive protein [14–16]. Median URR was determined from out-patient dialysis claims (minimum, three claims).

Data on dialysis units were obtained from the CDC annual survey of US dialysis centres [17]; these data included information on unit profit status (for-profit, not-for-profit), unit designation (freestanding or hospital-based), dialyser membrane usage, and use of germicide and bleach in the reuse process. Reuse practices were categorized according to germicide/bleach combination (formaldehyde with bleach, formaldehyde without bleach, glutaraldehyde with bleach, glutaraldehyde without bleach, peracetic acid with bleach and peracetic acid without bleach) and no reuse. The small number of units (81 of 3485; 2.3%) using Amuchina products (Amuchina International, Gaithersburg, MD, USA) or heat reuse were excluded from this study. The CMS dialysis provider number was used to link dialysis units to patients.

#### Statistical methods

Demographic and disease severity characteristics of patients in no-reuse units and units using each type of germicide/bleach combination were analysed by the chi-square test and least-significant-difference pairwise t-tests, with \( P < 0.05 \) considered statistically significant. Mortality risk was assessed with a Cox regression model, stratified on diabetic status to address proportionality [18] and bootstrapped at the dialysis-unit level, which determined the reuse practices to reduce the clustering effect. We adjusted for age, race, gender, unit profit status, unit designation, mean haematocrit level and EPO dose per month (as continuous variables), median URR, disease severity measures (number of blood transfusions and hospital days during the entry period) and 10 comorbid conditions. Risk of first hospitalization was assessed in the same fashion, excluding patients who were hospitalized at the beginning of the follow-up.

#### Results

Table 1 shows the process leading to the selection of the 49 273 study patients. Included in the analysis were all
patients who were incident during 1998 and 1999, survived the first 9 months of ESRD on haemodialysis, could be linked to a dialysis provider by means of CDC survey data identifying the reuse process, had at least four EPO and at least three URR claims, and were treated with single-use dialysers or dialysers reused after processing with formaldehyde, glutaraldehyde or peracetic acid (with or without bleach).

Table 2 provides the demographic characteristics of the patients in the various reuse groups. There were no statistically significant differences in gender or diabetic status between groups; differences in racial distribution were significant ($P=0.001$). The formaldehyde/bleach group was younger than other groups ($P<0.05$); the glutaraldehyde/bleach group was older than the peracetic acid/no-bleach and the no-reuse groups ($P<0.05$).

Figure 1 depicts the distribution of hospital-based and not-for-profit dialysis units according to reuse group. There was a significant difference ($P=0.001$) in the distribution of hospital-based and not-for-profit units in the various reuse groups. As shown, almost half of the hospital-based and not-for-profit units did not reuse dialysers during the study period.

### Table 1. Patient selection process

<table>
<thead>
<tr>
<th>Entry criteria</th>
<th>No. of patients meeting entry criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident HD patient survived 90 days</td>
<td>68 548 73 109 141 657</td>
</tr>
<tr>
<td>Survived 6 month entry period on HD</td>
<td>56 382 60 372 116 754</td>
</tr>
<tr>
<td>Linked to dialysis provider with CDC data</td>
<td>42 723 56 089 98 812</td>
</tr>
<tr>
<td>Had ≥4 EPO and ≥3 URR claims</td>
<td>20 745 30 434 51 179</td>
</tr>
<tr>
<td>On formaldehyde reuse, glutaraldehyde reuse, peracetic acid reuse, or no reuse</td>
<td>20 369 28 904 49 273*</td>
</tr>
</tbody>
</table>

HD, haemodialysis; CDC, Centers for Disease Prevention and Control; EPO, erythropoietin; URR, urea reduction ratio.

*Study group

### Table 2. Patient demographic characteristics by reuse group

<table>
<thead>
<tr>
<th>Reuse group</th>
<th>$n$</th>
<th>Age (mean ± SD, years)</th>
<th>Female (%)</th>
<th>Diabetic (%)</th>
<th>Race (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>White</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Black</td>
</tr>
<tr>
<td>Bleach</td>
<td>13 133</td>
<td>64.2 ± 14.7</td>
<td>49.0</td>
<td>47.2</td>
<td>58.2</td>
</tr>
<tr>
<td>No bleach</td>
<td>1804</td>
<td>65.4 ± 14.9</td>
<td>47.1</td>
<td>46.7</td>
<td>63.9</td>
</tr>
<tr>
<td>Glutaraldehyde</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Bleach</td>
<td>2452</td>
<td>66.1 ± 13.9</td>
<td>49.1</td>
<td>44.7</td>
<td>63.2</td>
</tr>
<tr>
<td>No bleach</td>
<td>714</td>
<td>65.3 ± 14.4</td>
<td>51.7</td>
<td>45.9</td>
<td>54.8</td>
</tr>
<tr>
<td>Peracetic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleach</td>
<td>1007</td>
<td>65.5 ± 14.3</td>
<td>49.3</td>
<td>47.7</td>
<td>60.5</td>
</tr>
<tr>
<td>No bleach</td>
<td>23 112</td>
<td>65.2 ± 14.6</td>
<td>48.8</td>
<td>46.9</td>
<td>62.0</td>
</tr>
<tr>
<td>No reuse</td>
<td>7051</td>
<td>64.7 ± 15.0</td>
<td>47.8</td>
<td>45.8</td>
<td>60.8</td>
</tr>
</tbody>
</table>

Fig. 1. Distribution of hospital-based and not-for-profit dialysis units according to reuse group. In general, the not-for-profit column includes patients represented in the hospital-based column, plus patients treated at not-for-profit, freestanding dialysis units. FB, formaldehyde with bleach; FN, formaldehyde without bleach; GB, glutaraldehyde with bleach; GN, glutaraldehyde without bleach; PB, peracetic acid with bleach; PN, peracetic acid without bleach; NR, no reuse.
Figure 2 shows the comparisons of reuse groups on the basis of clinical variables and disease severity measures. The range in mean haematocrit level (34.1–34.7%), while showing statistically significant differences that could affect the risk analysis, may not be clinically meaningful. Wide differences in mean monthly EPO dose were observed between reuse groups; doses ranged from 61,000 to 73,000 units per month. The percentage of patients with a median URR of <65% was lowest in the peracetic acid reuse groups and highest in the glutaraldehyde and no-reuse groups.

Groups were similar in number of comorbid conditions and number of hospital days, although some statistically significant differences were noted. The number of transfusions during the entry period was generally low, with glutaraldehyde reuse groups being the lowest and formaldehyde groups being the highest.

Figures 3 and 4 show the results of the Cox regressions for mortality and first-hospitalization risks, respectively. With respect to the hypothesis tested that outcomes are best in patients treated using dialysers cleaned with bleach and sterilized with...
formaldehyde, there were no significant differences in the mortality or first-hospitalization risk for patients in dialysis units not using bleach as a cleaning agent. Also, outcomes for patients treated in units using glutaraldehyde did not vary according to use of bleach (the small subset of patients treated in glutaraldehyde/no-bleach units had a non-significant lower risk). In the analysis of first-hospitalization risk, there was no difference according to the various germicide/bleach combinations. Overall, there was no significant difference between the reuse and no-reuse groups in hospitalization risk or relative risk of death.

Discussion

Our study tested the hypothesis that reuse of dialysers after processing with bleach and certain types of germicides, a practice that has been associated with improved or retained large-molecular-weight clearances, would also be associated with lower hospitalization risk and mortality in haemodialysis patients [19,20]. Our rationale for testing this hypothesis was that clinical practice has changed significantly during the past decade, particularly since the 1997 publication of the National Kidney Foundation-Dialysis Outcomes Quality Initiative (DOQI) clinical practice guidelines for dialysis therapy and anaemia treatment [10]. Observational studies from periods earlier than 1997 may be complicated by inconsistent care, which may impede interpretation of the findings [9,10]. To reduce potential biases related to inconsistent care, we analysed more recent data, using information on dialysis therapy as reported to CMS on dialysis claims and information on haematocrit levels as reported to CMS on EPO claims.

The overall analysis showed no significant difference in relative risk of death or in hospitalization risk among the reuse groups (including the no-reuse group) according to use or non-use of bleach in the cleaning process. More specifically, with formaldehyde/bleach reuse of dialysers considered as the baseline, formaldehyde/no-bleach reuse carried a relative risk of death of 1.002 (95% CI, 0.92–1.10). No-reuse units had a non-significant 3% higher risk of death. On the basis of these observations, there appears to be no evidence during the 1998–1999 period that reuse practices, either in general or associated with bleach, carried a survival advantage or disadvantage.

Hospitalization risk was evaluated as a more sensitive indicator of patient outcome because hospitalization is five times more likely than death in haemodialysis patients. There was no significant difference in risk of first hospitalization between the formaldehyde/bleach group (used as the baseline) and the various germicide/bleach combinations. These findings are consistent with the findings of the mortality analysis. Taken together, the findings of our mortality and hospitalization risk studies indicate that reuse practices in general, and germicide/bleach cleaning practices in particular, are not associated with a significant effect on patient mortality or hospitalization risk in the United States.

The findings we report stand in direct contrast to those reported by Port et al. [9], who studied 12 791 patients who were prevalent on December 31, 1993, and were followed for mortality events through 1994. Like us, Port et al. [9] found no significant differences between reuse and no-reuse units. However, they did find that units practising reuse with formalin and bleach had a significantly lower risk of death, lower even than the risk for no-reuse units. There was no explanation for the observation of better outcomes in the reuse units compared with the no-reuse units when adjusted for dialysis therapy and other clinical factors. Differences between their findings and ours may reflect differences in the quality of care given in 1993–1994 (the period covered by the Port et al. [9] study) and 1998–1999 (the period covered by our study). From the early 1990s through the year 2000, significant improvements in dialysis therapy and haematocrit level have been noted [21]. Through the year 2000, the number of patients achieving a single-pool Kt/V ≥ 1.2 increased from 74 to 86%. Between 1996 and 2000, the mean Kt/V increased from 1.34 to 1.49.
During that shorter period of time between 1997 and 2000, the percentage of patients with haemoglobin levels of ≥11 g/dl increased from 43% in 1997 to 74% by 2000, with the mean haemoglobin level reaching 11.4 g/dl in the last quarter of 1999, close to the midpoint of the DOQI guidelines. Because provider-associated indicators of care vary significantly in the United States, as recently reported in the USRDS 2002 Annual Data Report (pages 182 and 183, figures 11.14 and 11.15) [1], shifts in clinical practices during the 5–6 years of the period studied by Port et al. [9] may have had significant effects on the associated mortalities. Even within the year 2000, mean haemoglobin levels varied significantly between provider chains. Other clinical practices, such as influenza vaccinations, which have been shown to be associated with lower hospitalization rates and improved survival rates [22], also varied significantly between providers. On the basis of these observations and the more complete characterization of dialysis providers, there appears to be no survival advantage based on type of reuse practice, germicide used or bleach cleaning.

Our findings are consistent with the results recently reported by the investigators of the HEMO trial, a randomized controlled trial assessing dialysis with high- and low-flux dialysers and a lower and higher Kt/V. The trial found no difference in mortality or hospitalization on the basis of large-molecular-weight clearances [23]. Given that the HEMO trial found no difference in outcome based on membrane flux and that a randomized controlled trial found no effects of flux, results confirmed in our recent study [24], it is possible that earlier studies were subject to unrecognized biases. In fact, more recent studies by Port et al. [9] found no effect of bleach reuse.

In the current study, we attempted to avoid limitations seen in previous studies by our group and by others. Because of the large sample size in this study, we had a greater opportunity to characterize dialysis units and their reuse practices. The use of adjustments for dialysis therapy and haematocrit level also strengthens the findings. The study of incident cohorts, as opposed to prevalent cohorts, reduced the potential biases of patient duration on dialysis, a limitation inherent in analyses of prevalent patients. The bootstrapping method used, as introduced by Feldman et al. [3], provided more realistic confidence intervals, based on the unit-level analysis, and reduced the potential biases of a patient-level analysis, since reuse practices tend to be unit wide.

Limitations in the present study should be considered and addressed in future studies of this type. There was no CDC surveillance survey of dialysis providers in 1998. Therefore, we had to study 1997 and 1999 providers, matching dialysis units according to their characteristics to reduce the likelihood of including units that had switched reuse methods between the 2 years. This reduced the number of individuals in the 1998 cohort by 24%, whereas only 7% of patients in the 1999 cohort were lost because we could not link individual patients to their dialysis providers. Because the CDC has conducted surveys each year since 1999, gathering data that includes information on germicides and bleach cleaning, the present study should be repeated to ensure that outcomes were consistent for the years 1999, 2000 and 2001. Other biochemical variables, such as serum albumin level and residual renal function at initiation of dialysis, were not included in the present analysis because of concern that the attempt would require a further reduction in cohort size.

Because the data after 1999 are more complete, the variables available on the Medical Evidence Report at initiation of dialysis should be included in future analyses to ensure that incident patients are characterized on the basis of complexity of disease and provider reuse practices. Long-term follow-up studies are needed; these could be performed for the most recent era of clinical practice guidelines. Such a study would provide a better indication of the effect of consistent reuse practices on hospitalization risk and mortality.

In conclusion, our study of 1998 and 1999 incident Medicare haemodialysis patients found no significant differences in mortality and hospitalization risk between patients receiving dialysis in reuse units and those treated in no-reuse units. We also found no significant differences in outcomes associated with particular germicides or germicide/bleach combinations. These findings may reflect the National Kidney Foundation’s 1997 introduction of clinical practice guidelines, the intent of which was to bring about increased consistency of care. Long-term studies of incident patients treated with consistent reuse practices should be conducted in the future, now that variation in clinical practices has narrowed in the United States.

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