Septicemia in Patients with ESRD Is Associated with Decreased Hematocrit and Increased Use of Erythropoietin

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Septicemia, a common complication in chronic dialysis patients, may be an important factor in erythropoietin (EPO) hyporesponsiveness, because it is a form of inflammation. The quantitative impact of septicemia on EPO requirements has not been studied. The purpose of this study was to analyze patterns of EPO use and levels of anemia among patients who had ESRD and were hospitalized with septicemia. Using United States Renal Data System data, septicemia admissions were identified in patients with first ESRD service from 1996 to 2001. Mean EPO dosage and hematocrit (Hct) level were analyzed from 2 mo before until 3 mo after admission and compared with patients who were hospitalized with acute myocardial infarction (AMI) and patients with no hospitalizations. A total of 4640 hospitalized patients were included in the analysis: 3975 for septicemia and 665 for AMI. In both groups, mean Hct declined significantly in the month of admission and increased in the second month after admission. At all time points, both groups had significantly lower Hct levels compared with the nonhospitalized group. Mean EPO dosage increased, most rapidly in the month after admission. EPO use was highest in the septicemia group. Hospitalization with septicemia is associated with worsening anemia and increasing EPO use. This also was observed for patients who were hospitalized with AMI, suggesting that acute intercurrent illness plays an important role in EPO hyporesponsiveness. Strategies to prevent septicemia are important not only to decrease clinical morbidity but also to conserve EPO usage and thus contain the costs of care for this complex patient population.


Materials and Methods

Study Design and Patient Selection

This retrospective cohort study used the United States Renal Data System (USRDS). Hospitalizations were identified on the basis of Medicare hospital claims using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) and/or Diagnosis Related Group (DRG) (16) codes for discharge diagnoses.

This study compared patterns of EPO use and hematocrit (Hct) among patients who were hospitalized with septicemia with two comparison groups: Patients who were admitted with another acute illness (acute myocardial infarction [AMI]) and patients who were not recently hospitalized for any acute clinical event. Inpatient septicemia admissions (ICD-9-CM 038.xx) were identified with a first ESRD service date between January 1, 1996, and September 30, 2001. Admissions were included when (1) the dialysis modality at admission was recorded as hemodialysis, (2) Medicare was the primary payer for the admission, (3) the admission occurred after the date of first ESRD service, and (4) the dialysis monthly billing period ended before or during the hospitalization (to ensure that the outpatient EPO treatment for the month in which the patient was hospitalized occurred immediately before the admission). We also studied patients who were hospitalized with AMI and patients with no hospitalization to understand whether patterns of EPO dosage and level of anemia were unique to the septicemia group. Inpatient AMI admissions (DRG codes 121 to 123), excluding bypass surgery (ICD-9-CM 36.1, 36.10 to 36.17, and 36.19), were identified during the same period as described above. Because patients who had bypass surgery could have experienced decreased Hct as a result of blood loss, we excluded them from the analyses. After identifying the septicemia and AMI groups, we determined mean time from start of dialysis to hospitalization and used it to define the time period for...
sampling the nonhospitalized group. This resulted in identification of patients without a hospitalization during the 15- to 21-mo period after the date of first ESRD service.

Data

Basic demographic data consisted of patient age at the time of hospitalization, race, and gender. Average length of stay (LOS) was calculated for the septicemia and AMI admissions. Vascular access type was determined by identification of the Healthcare Common Procedure Coding System (17) code for the vascular access procedure that occurred closest in time before the septicemia or AMI admission or closest in time to the middle of the observation period in the nonhospitalized group (18 mo after first ESRD service). Clinical history, as recorded at the time of the first ESRD service, was examined using the Medical Evidence Form that was completed by the patient’s physician. Conditions that were recorded were alcohol dependence, cancer, cardiac arrest, congestive heart failure, cerebrovascular disease, diabetes (insulin dependent), diabetes as primary or contributing cause of ESRD, drug dependence, cardiac dysrhythmia, hypertension, ischemic heart disease, myocardial infarction, incontinßity to ambulate, inability to transfer, EPO use (predialysis), chronic obstructive pulmonary disease, and peripheral vascular disease. Cause of renal failure also was examined using the Medical Evidence Form.

Charlson comorbidity index (CCI) scores, a method of classifying prognostic comorbidity, were calculated on the basis of diagnosis codes and procedures that were reported during 1 yr before index hospitalization. The Dartmouth-Manitoba version (18,19), with modifications to reflect more recently developed codes, was used to access the severity of comorbidity.

Mean EPO dosage and level of anemia (defined according to Hct) were recorded from 2 mo before hospitalization to 3 mo after admission to understand the correlation of EPO dosage and level of anemia with septicemia hospitalization. EPO dosage and Hct level were determined on the basis of the dialysis center report that was submitted to Medicare with the claim. To ensure that the outpatient EPO treatment for the month in which the patient was hospitalized (t0) occurred immediately before the admission, we included only the admissions that overlapped with dialysis monthly billing period. Therefore, hospitalization (t0) contained two distinct periods: (1) Outpatient treatment before the admission and (2) the admission itself. As a result, exposure time to EPO varied for each patient depending on the timing of admission in the month. For example, for a person who was admitted at the end of the month, the exposure time was longer compared with a person who was admitted at the beginning of the month. Mean EPO dosage was calculated using the total dosage given during each billing period (on monthly basis) divided by the reported number of injections. Hct levels were determined from the monthly dialysis center report that was submitted to Medicare.

Statistical Analyses

Univariate and bivariate statistics were used to examine differences in patient demographics among septicemia, AMI, and nonhospitalized groups. Continuous variables were summarized by the mean and SD, whereas discrete data or counts were summarized using percentages.

Differences in EPO dosage and Hct level between time points were calculated for the septicemia, AMI, and nonhospitalized groups. Patients with septicemia and AMI were divided further into two subgroups using their median LOS: (1) Shorter LOS (septicemia LOS <9 d; AMI LOS <6 d) and (2) longer LOS (septicemia LOS ≥9 d; AMI LOS ≥6 d). It was hypothesized that LOS might function as a proxy for severity of illness during the admission and that greater severity might have a greater impact on level of anemia and EPO usage. Differences in EPO dosage and Hct level between patients with shorter versus longer hospital stays were examined. T tests (20) were conducted to determine differences in EPO dosage and Hct levels between groups and time points. Changes in Hct levels and EPO dosages over time were tested for significance using ANOVA (21) with repeated measures. SAS statistical software 8.2 (SAS Institute, Cary, NC) was used to conduct the analyses.

Results

Characteristics of the Sample

A total of 4640 hospitalized patients (3975 septicemia and 665 AMI) and 103,397 nonhospitalized patients were included in the analysis. Characteristics of this study population are shown in Table 1. The three groups were similar in terms of demographics, although the AMI group was significantly older. Catheter was the most common type of vascular access for the three groups. The septicemia group had a significantly longer LOS than the AMI group (12.2 versus 7.5; P < 0.0001). The CCI score was found to be higher in the AMI group (7.0). However, the CCI includes myocardial infarction (Charlson weight = 1), which skews the comparison. Diabetes (type 2) was the leading cause of renal failure and was followed closely by hypertension.

In terms of clinical conditions that were recorded at the time of first ESRD service, the septicemia and AMI groups seemed similar. The nonhospitalized group was less likely to have congestive heart failure, diabetes (insulin dependent), chronic obstructive pulmonary disease, and peripheral vascular disease compared with the septicemia group.

Level of Anemia and Patterns of EPO Usage

Level of Anemia. Mean Hct decreased in the month of hospitalization and increased in the second month after hospitalization in both the AMI and septicemia groups (Figure 1). Changes in mean Hct over time within the groups were significant (P < 0.0001), with the greatest impact in both groups occurring in the month after hospitalization. Mean Hct values were significantly lower in the septicemia group than in the AMI group until 2 mo after hospitalization (P < 0.05). In the nonhospitalized group, Hct was relatively stable over time and was significantly higher than in the septicemia and AMI groups during the entire observation period (P < 0.05). The pattern of change in Hct across time points did not differ between the two hospitalized groups.

Mean Hct was significantly lower in the longer LOS septicemia group than in the other groups at each time point (P < 0.05; Figure 2). Differences between longer and shorter LOS in Hct level were significant in the septicemia (P < 0.05) but not in the AMI group. It seems that LOS has greater impact on Hct in the septicemia group than in the AMI group.

EPO Usage. Mean EPO dosage increased over time for the septicemia and AMI groups, with the largest increase occurring 1 mo after hospitalization (Figure 3). EPO dosage slowly decreased over time in the nonhospitalized group. Changes in EPO use across time points within the septicemia and AMI groups were significant (P < 0.0001), but they were NS within...
the nonhospitalized group. EPO use was significantly higher in the septicemia group than in the AMI group from the time of hospitalization through 2 mo after hospitalization (P < 0.05). Differences between the septicemia and AMI groups in EPO dosage changes across time points were significant only in the month before hospitalization, with a mean increase of 164 units in the septicemia group and a mean decrease of 155 units in the AMI group (P = 0.0263).
Long versus short LOS had a greater impact on EPO use in the septicemia group than in the AMI group (P < 0.05 after hospitalization; Figure 4). Mean EPO dosage increases were similar across shorter and longer LOS groups for those who were hospitalized with septicemia, but the patients with longer LOS consistently required higher dosages over time, particularly around the hospitalization. For both shorter and longer LOS AMI groups, EPO dosage was lower than both the shorter and longer LOS septicemia groups (except at the beginning and the end of the observation period). The difference in change in EPO dosage, measured by the Δ between time periods, was significant only for the septicemia group during the time period from hospitalization to 1 mo after hospitalization, with the shorter LOS septicemia group having a Δ of 382 units and the longer LOS septicemia group having a Δ of 977 units (P < 0.0003).

**Discussion**

This study confirmed our hypothesis that septicemia is associated with EPO hyporesponsiveness. We observed that in patients with ESRD and with septicemia, Hct levels fell and EPO dosage increased in the time period surrounding hospitalization. In general, patterns of EPO use and Hct were found to be similar for patients with septicemia and with AMI, and both groups differed significantly from the nonhospitalized control subjects. Within-group changes of EPO use differed significantly between septicemia and AMI groups only in the month before hospitalization. Although the difference between time points in Hct levels and EPO dosages were similar for the septicemia and AMI groups, we observed that absolute values of Hct levels were significantly lower for the septicemia group from 2 mo before hospitalization (P < 0.05), and EPO dosages were significantly higher from hospitalization through 2 mo after hospitalization. These findings suggest that hospitalization for an acute illness affects the level of anemia and EPO usage and that an infection may have a greater impact on both.

To explore this relationship further and test for a dosage response, we hypothesized that if EPO resistance were related to an acute illness, then a more severe illness might have greater impact than a less severe one. Using median LOS as a proxy for disease severity, we found that septicemia patients with longer LOS had substantially lower Hct levels and higher EPO dosages compared with the shorter LOS group. The differences in Hct levels and EPO dosages between the longer and shorter LOS AMI groups were less pronounced. Perhaps LOS does not reflect illness severity as accurately in this latter population.

Our findings add to previously published work in this area. Several studies suggested that either chronic or acute inflammation leads to inadequate EPO response in hemodialysis patients, which was shown by measuring markers of inflammation (e.g., levels of serum C-reactive protein) (5,10–12). An important finding of our study was the strong association between EPO hyporesponsiveness and the specific cause of inflammation (i.e., septicemia). One retrospective chart audit of 65 patients concluded that hemodialysis patients experience a significant and prolonged decrease in Hb levels and an increase in EPO requirements after hospitalization (22). However, they did not find that inflammation had a significant impact on either Hb levels or EPO dosage. One possible confounding factor may be that more patients in the noninflammatory group underwent surgery during hospitalization, suggesting that the
patterns of EPO use and hematocrit associated with septicemia

As with all studies, there are limitations to our findings and to our approach. First, the Hct and EPO dosage data in the USRDS are available only at monthly intervals as required by Medicare for reimbursement purposes. Although these data likely are accurate (because they are critical to reimbursement), they lack the “granularity” that might result from more frequent points of observation. Nevertheless, we do not believe that more frequent points of observation would change the overall conclusions of our study. Second, the USRDS does not contain Hct values that were measured during the hospitalization or dosages of EPO that might be provided. Given that the period of observation spans several months, we also do not believe that data from the hospital itself would fundamentally change the findings. Moreover, our restriction to billing periods that ended before or during the hospitalization seems to alleviate any potential problems. Despite these possible limitations, the results should have generalizability because our analysis was conducted among a very large sample of hemodialysis patients who had ESRD and were hospitalized for septicemia.

Our approach may underestimate the differences in EPO dosage before and after septicemia hospitalization, as the average EPO usage was not adjusted for patient weight or for whether the patient received transfusions. Patients with ESRD tend to lose weight as a result of poor intake of protein and calories during the course of chronic kidney disease. In addition, if patients received transfusions, then changes in EPO dosage would underestimate the impact of inflammation on EPO hyporesponsiveness.

Conclusion

This study provides the first quantitative assessment of EPO usage and level of anemia in patients who had ESRD and were hospitalized for septicemia. Our findings suggest that intercurrent events in patients with ESRD have a clinically important impact on the patients’ ability to produce red blood cells. These clinical consequences also result in the additional economic cost of increasing the EPO dosage, which seems to persist for a substantial amount of time. Strategies to prevent septicemia (or AMI) are important not only to decrease clinical morbidity but also to optimize treatment with EPO and thus constrain the costs of care.

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References