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Original Investigation

Comparative Effectiveness of Iron and Erythropoiesis-Stimulating Agent Dosing on Health-Related Quality of Life in Patients Receiving Hemodialysis

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Background: The potential effects of iron-dosing strategies and erythropoiesis-stimulating agents (ESAs) on health-related quality of life (HRQoL) in the dialysis population are unclear. We examined the independent associations of bolus versus maintenance iron dosing and high versus low ESA dosing on HRQoL.

Study Design: Retrospective cohort design.

Setting & Participants: Clinical data (2008-2010) from a large dialysis organization merged with data from the US Renal Data System. 13,039 patients receiving center-based hemodialysis were included.

Predictor: Iron and ESA dosing were assessed during 1-month (n = 14,901) and 2-week (n = 15,296) exposure periods.

Outcomes: HRQoL was measured by the Kidney Disease Quality of Life (KDQOL) instrument (0-100 scale) during a 3-month follow-up period.

Measurements: Generalized linear mixed models, adjusting for several covariates, were used to estimate associations between iron and ESA dosing and HRQoL overall and for clinically relevant subgroups.

Results: For the 1-month exposure period, patients with lower baseline hemoglobin levels who received higher ESA dosing had higher physical health and kidney disease symptom scores (by 2.4 [95% CI, 0.6-4.2] and 5.6 [95% CI, 2.8-8.4] points, respectively) in follow-up than patients who received lower ESA dosing. For the 2-week exposure period, patients with low baseline hemoglobin levels who received bolus dosing had higher mental health scores (by 1.9 [95% CI, 0.0-3.8] points) in follow-up. Within the low-baseline-hemoglobin subgroup, individuals with a catheter or dialysis vintage less than 1 year who received higher ESA dosing had higher HRQoL scores in follow-up (by 5.0-9.9 points) and individuals with low baseline transferrin saturations who received bolus dosing had higher HRQoL scores in follow-up (by 2.6-5.8 points).

Limitations: Observational design; short duration of observation.

Conclusions: For individuals with low baseline hemoglobin levels, higher ESA dosing and bolus iron dosing were associated with slightly higher HRQoL scores in follow-up. These differences became more pronounced and clinically relevant for specific subgroups.

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INDEX WORDS: Health-related quality of life (HRQoL); hemodialysis (HD); anemia; erythropoiesis-stimulating agent (ESA); intravenous iron; dosing pattern; bolus dosing; maintenance dosing; epoetin alfa; hemoglobin; transferrin saturation (TSAT); chronic kidney disease (CKD); end-stage renal disease (ESRD).

End-stage renal disease (ESRD) is a chronic debilitating condition that significantly affects health-related quality of life (HRQoL). Common medical problems such as anemia, hypertension, malnutrition, cardiovascular disease, mineral bone disorders, pain, and depression affect both physical and mental health in this population.[1-5] Dietary restrictions, time demands of dialysis, and physical limitations caused by the disease may disrupt personal and social relations.[4-6] Lower levels of HRQoL have also been shown to be associated with hospitalization and mortality in patients with ESRD.[5,7-9]

Appropriate anemia management is considered one approach to maintaining or improving HRQoL in

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patients with ESRD.[10] Erythropoiesis-stimulating agents (ESAs) and intravenous iron are used in combination to treat the anemia of ESRD.[11,12] Although several studies have correlated anemia with decreased HRQoL in patients with ESRD,[4] controversy remains over the effectiveness of ESAs in improving HRQoL in the ESRD population. Much of the current debate focuses on the appropriate target hemoglobin level.[13-15]

Information on the effectiveness of intravenous iron in improving HRQoL in patients with ESRD is also lacking. Two general dosing strategies are used to deliver intravenous iron. Iron may be delivered in large intermittent doses to replenish diminished iron stores (bolus dosing) or in low regular doses to maintain iron stores (maintenance dosing).[16,17] The DRIVE (Dialysis Patients' Response to IV Iron With Elevated Ferritin) trial, which evaluated the efficacy of intravenous ferric gluconate in anemic hemodialysis patients with high ferritin levels and low transferrin saturations (TSATs), indicated that administration of a large repletion dose of intravenous iron (1 g delivered in 125-mg doses over 8 consecutive sessions) improved hemoglobin levels relative to levels in no-iron controls.[18] Other studies have also demonstrated a beneficial effect of bolus dosing on anemia management parameters.[16,17,19] However, HRQoL was not assessed in any of these studies.

To further our understanding of the potential independent effects of intravenous iron and ESA dosing on HRQoL, we conducted an observational study of a cohort of patients receiving in-center hemodialysis. Specifically, we examined the short-term effects of iron dosing pattern (bolus or maintenance) and ESA dosing (high vs low) on HRQoL.

METHODS

Data Sources

This study was approved by the University of North Carolina's Institutional Review Board. Data for this study came from the clinical database of a large US dialysis organization and the US Renal Data System (USRDS). The clinical database contains information for patients treated at approximately 1,500 outpatient dialysis facilities in the United States. Clinical, laboratory, and treatment data are captured using standardized electronic data entry. We used the clinical database to obtain detailed information for iron use/dosing, ESA (epoetin alfa) use/dosing, clinical laboratory values (eg, hemoglobin and TSAT), vascular access, and self-reported HRQoL. These data were merged with USRDS data, which includes demographic, health care, comorbid condition, and clinical information.[20] We analyzed data from 2008 to 2010, based on data availability and the period during which HRQoL measurements were collected by the dialysis organization (ie, 2009-2010).

Study Design

We used a retrospective cohort design with a 1-month exposure assessment period (for ESA and iron), preceded by a 6-month baseline period for covariate assessment and followed by a 3-month follow-up period for outcome assessment. Such a design (ie, baseline, exposure, and assessment periods distinct and not overlapping) minimizes many sources of bias common in nonexperimental longitudinal designs. The index date of the exposure period was anchored on a TSAT value because this information guides iron administration and hemoglobin was almost always measured at the same time (98% of the time). Because questions on the HRQoL instrument ask patients to think about their health over the past 4 weeks, the HRQoL measure occurred within the second or third month of follow-up to avoid overlap with the exposure period (Fig 1). To assess the effects of shortening the exposure and follow-up times, we conducted 3 sensitivity analyses: (1) 2-week exposure/3-month follow-up, (2) 1-month exposure/2-month follow-up, and (3) 2-week exposure/2-month follow-up. By shortening the exposure window, we assessed whether the effects of iron/ESA dosing over a 2-week period (vs 1 month) had a larger or smaller impact on HRQoL. By shortening the follow-up period, we assessed whether iron/ESA dosing had a larger or smaller effect when looking at outcomes more proximal to the dosing.

Cohort Identification

We limited our sample to center-based hemodialysis patients with continuous Medicare coverage who had been on dialysis therapy for at least 9 months. The 9-month period accounted for the 6-month baseline period and an additional 3 months from dialysis therapy initiation to allow for stability in processing Medicare claims.[20] Patients also had to have at least one TSAT measurement on which to anchor the exposure period and a subsequent HRQoL measurement during the second or third month of follow-up. Eighteen percent of patients in the clinical database had HRQoL measurements. Most patients had one HRQoL measurement per year, although a small percentage had 2 or 3 measurements per year. Individuals with polycystic kidney disease were excluded because the anemia management of these patients differs greatly from that of most patients with ESRD receiving hemodialysis.

TSAT measurements were eligible if they occurred between November 3, 2008, and October 31, 2010 (to allow for the 1-month exposure period, the 1-month lag period, and at least 1 day of follow-up in 2009 or 2010), and had an accompanying HRQoL measurement. TSAT measurements were excluded if: (1) iron dextran was administered during the exposure period; (2) there was an insufficient duration of Part A claims at baseline (ie, $<$120 days of Part A claims), suggesting incomplete data; or (3) there were fewer than 9 dialysis sessions in the last month of baseline or during the exposure period. (The third restriction avoided incomplete data; for example, we did not have exposure information for hospitalized patients.) We also excluded TSAT records with missing covariate information and TSAT measurements that occurred in the follow-up period of a prior eligible TSAT. Eligible patients therefore could contribute more than one observation if another TSAT measurement occurred after the follow-up period of a prior eligible TSAT (Fig 1).

Study Variables

Outcomes

HRQoL was measured using the RAND version of the Kidney Disease Quality of Life (KDQOL-36) Survey,[21] a 36-item survey with 5 subscales. We used measures from 3 of the 5 subscales: the 12-item Short Form Health Survey (SF-12) measure of physical health, the SF-12 measure of mental health, and the symptoms and problems subscale, which assesses how bothered the respondent is with the symptoms of kidney disease (eg, shortness of breath and fatigue). These 3 subscales address health aspects likely affected by anemia and assess the patient's recent health by asking about their health over the past 4 weeks. Each subscale is scored on a scale of 0 to 100, with higher scores indicating better health. Three