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Original Investigation

Red Blood Cell Survival in Long-term Dialysis Patients

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Background: Shortening of red blood cell (RBC) survival contributes to the anemia of chronic kidney disease. The toxic uremic environment accounts for the decreased RBC life span. The contribution of mechanical damage caused by hemodialysis to the shortened life span is unclear. Reductions up to 70% in RBC survival have been reported in uremic patients. To date, no accurate well-controlled RBC survival data exist in dialysis patients treated using different dialysis modalities and receiving erythropoiesis-stimulating agent (ESA) therapy. The aim of this study was to determine RBC survival in hemodialysis (HD) and peritoneal dialysis (PD) patients compared with healthy persons.

Study Design: Observational study.

Setting & Participants: 14 HD patients and 5 PD patients were recruited from the dialysis unit. Healthy volunteers (n = 14) age- and sex-matched to HD participants were included. All dialysis patients received either ESA therapy or regular iron supplementation.

Predictor: Dialysis patients versus age- and sex-matched healthy controls.

Outcomes: RBC survival.

Measurements: RBC survival was determined using radioactive chromium labeling.

Results: More than 85% of dialysis patients were anemic (hemoglobin, 12.0 ± 1.1 g/dL); hemoglobin concentrations were not significantly different between HD and PD patients. Median RBC survival was significantly decreased by 20% in HD patients compared with healthy controls: 58.1 (25th-75th percentile, 54.6-71.2) versus 72.9 (25th-75th percentile, 63.4-87.8) days ($P = 0.02$). No difference was shown between the PD and HD groups: 55.3 (25th-75th percentile, 49.0-60.2) versus 58.1 (25th-75th percentile, 54.6-71.2) days ($P = 0.2$).

Limitations: Label loss from RBCs associated with the chromium 51 labeling technique needs to be accounted for in the interpretation of RBC survival data.

Conclusions: Despite current ESA therapy, decreased RBC survival contributes to chronic kidney disease–related anemia, although the reduction is less than previously reported. There does not appear to be net mechanical damage associated with HD therapy resulting in decreased RBC life span.

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INDEX WORDS: Red blood cell survival; chronic kidney disease; anemia; hemodialysis; peritoneal dialysis; uremia.

Normocytic normochromic anemia is a common finding in patients with chronic kidney disease (CKD), contributes to the burden of the disease, and is associated with patients' morbidity and mortality.[1] The prevalence of anemia increases with decreasing kidney function and becomes almost universal in patients with end-stage renal disease.[2,3] Anemia associated with kidney disease is caused predominantly by impaired erythropoiesis due to inadequate erythropoietin production. Other important mechanisms contributing to renal anemia include uremic toxins suppressing bone marrow function, substrate deficiencies, and shortened red blood cell (RBC) survival.[4-7] Impairment in RBC survival has been largely neglected in recent years, possibly due to the success of erythropoiesis-stimulating agents (ESAs).

Numerous studies have reported a significant decrease in RBC survival, ranging from one-third to two-thirds of normal survival.[7-12] RBC survival data derived from most of these studies are not comparable because they use different methods to measure survival, often include no controls, and involve a small number of participants with varying decreases in kidney function.

Decreased RBC life span appears to be caused by extracellular factors rather than an intrinsic cell defect, as shown in cross-transfusion experiments. When RBCs from uremic patients were transfused into healthy recipients, RBC survival improved, whereas healthy compatible RBCs had impaired survival when donated to uremic patients.[7,13] Although the exact

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mechanism for this is poorly understood, it is postulated that the uremic environment has a key role. From this aspect, an increase in RBC osmotic fragility,[14] disturbed RBC membrane phospholipid asymmetry,[15] and impaired RBC deformability[16] have been observed in uremic patients and may give rise to decreased RBC survival. Hemodialysis (HD) by itself also may contribute to the decrease in RBC survival because of mechanical damage induced by the dialysis membrane and extracellular circulation. A slight increase in RBC destruction occurring intermittently during HD has been observed without leading to a direct impact on hemoglobin concentrations.[11] Consequently, RBC survival in patients on HD therapy may be decreased to a greater extent compared with their counterparts on peritoneal dialysis (PD) therapy, who lack this form of mechanical damage, but still retain a uremic environment.

Currently, standard treatment with ESAs has improved the anemia associated with kidney disease substantially, and most patients on renal replacement therapy now receive this form of treatment regularly to maintain hemoglobin concentrations within the recommended target range.[17] The impact of ESA therapy on mature erythrocytes and their life span is speculative. Likewise, it has not yet been elucidated whether maintenance treatment with ESAs improves RBC survival in patients receiving long-term dialysis therapy.

Determining the RBC life span in healthy populations and patients with disease states is restricted by the lack of a simple and reliable method. The technique most widely used is the random-labeling method in which RBCs are tagged with radioactive chromium (^{51}Cr), such that disappearance of the label reflects loss of RBCs. This method provides data that often are confounded with other processes, such as loss of the label due to elution, that is, dissociation of ^{51}Cr from the hemoglobin, and potential loss of ^{51}Cr-bound hemoglobin due to RBC vesiculation.[18-20] The extent of elution varies depending on the labeling technique used and also under certain hematologic conditions. Vesiculation has not been taken into account in previous RBC survival studies because it has been identified only recently. Consequently, this method provides only relative RBC survival and the survival rate obtained is comparable to only other survival rates measured in the same study.

This study aims to challenge the current dogma that RBC survival is substantially decreased and contributes to anemia in HD patients who are undertaking extended dialysis regimens and using ESA therapy. Although previous studies have investigated RBC survival in HD patients on ESA therapy,[21,22] no healthy age- and sex-matched adults were included for comparison. In addition, to investigate the effect of mechanical damage associated with the dialysis procedure on RBC life span, RBC survival is explored in PD patients.

METHODS

Study Design

This was an observational study assessing RBC survival in patients receiving long-term dialysis (HD or PD) therapy and healthy participants. Patients were recruited directly from the Southern District Health Board Dialysis Unit. Dialysis patients were stratified according to dialysis modality (HD or PD) and healthy participants were included in the third arm of the study. This study was approved by the Lower Southern Region Ethics Committee (Dunedin, New Zealand), and all patients gave written informed consent to participate. This trial was conducted in accordance with the principles of the Declaration of Helsinki and is registered with the Australian New Zealand Clinical Trials Registry: ACTRN12610000145000.

Participants

Persons older than 18 years who had been established on maintenance HD or PD therapy for at least 3 months were eligible to participate in this study. Eligible patients had a cause of anemia that was secondary to CKD and a blood hemoglobin concentration within the range of 11.0-13.0 g/dL. All participants were either using a stable dose of ESA or received regular doses of iron supplements. Healthy volunteers with kidney function (defined as glomerular filtration rate $>$60 mL/min/1.73 m^2) and hemoglobin concentrations within the reference range were invited to enroll in this study and were matched according to age and sex to HD patients.

Exclusion criteria for all persons were active bleeding, blood transfusion of whole blood or RBCs within 30 days before study entry, concurrent malignancy, diabetes mellitus, uncontrolled hypertension, and clinical evidence of acute infective or inflammatory response at the time of study enrollment. For dialysis patients, lack of ESA or iron supplementation or dosage modification 30 days preceding study entry resulted in exclusion. Women of childbearing age were not invited to participate in this study. Basic clinical and demographic data were recorded and all participants underwent analysis of a full blood cell count before study enrolment.

HD and PD

Individualized dialysis conditions and regimens remained unchanged throughout the study. All HD patients used Fresenius 4008B machines (Fresenius Medical Care AG, www.fresenius.com) and a high-flux polysulfone membrane (FX60-100; Fresenius Medical Care AG). Dialysate water was derived from a central reverse-osmosis unit (Fresenius Medical Care AG) that removes $>$99% of all bacteria and pyrogens. The water supply to dialysis machines was tested regularly for bacterial contamination and met current Association for the Advancement of Medical Instrumentation Hemodialysis Water Quality (AAMI) criteria ($<$200 microbial counts/mL). HD access was through native arteriovenous fistulas, constructed from synthetic grafts or tunneled catheters. All PD patients were on continuous ambulatory PD therapy using Freeline Solo systems (Baxter Healthcare, www.baxter.com).