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The Use of Erythropoietin-Stimulating Agents Versus Supportive Care in Newborns with Hereditary Spherocytosis: A Single Center's Experience

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Abstract

Hereditary Spherocytosis (HS) is a common hemolytic anemia in which 75% of cases are autosomal dominant. Since most newborns with HS have a family history of disease, hematologists often see these infants before their physiologic hemoglobin nadir, which is exaggerated in comparison to healthy infants. The objective of this study was to evaluate the frequency of implementation and cost of erythropoietin-stimulating agents (EPO) versus transfusion in infants with HS at a single pediatric program. In the last decade, only 15% of infants with HS at our center have been treated with EPO, which costs twice that of a single transfusion and EPO treated infants did not always avoid transfusion. Infrequent prescription of EPO therapy to infants with HS at our center may be related to the incomplete data supporting its use.

Keywords

Pediatric; Hereditary Spherocytosis; Erythropoietin

Introduction

The physiologic anemia of infancy typically causes an asymptomatic anemia associated with low erythropoietin production and reticulocytopenia (1). In infants with HS, including those with mild or moderate HS later in childhood, the hemoglobin nadir is often more pronounced and persistent (i.e., both deeper and broader than normal), leading to symptomatic anemia requiring red cell transfusions during the first six months of life (2). The persistence and severity of the hemoglobin nadir in infants with HS may be due to both increased splenic filtering after birth as well as physiologic decreased production of erythropoietin. Compensated hemolysis in HS, a balance of reticulocytosis with hemolysis, has been shown to be, at least partially, due to elevated erythropoietin (3, 4). This change in

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Declaration of Interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

erythropoietin production during the first year of life may explain the severity of anemia in HS in the first year compared to later in life.

In 2000, an international group published a report of 16 anemic infants with HS treated with EPO (1000 IU/kg/week); in this study, 63% of infants did not require further transfusions after starting EPO, but 50% of infants received transfusions before EPO (5). Since report of this trial, case reports have been published on the use of EPO therapy to prevent transfusions in infants with HS (6–8). Given these reports as well as reports of EPO used to prevent transfusions in isoimmunization of the newborn, the hematologists at our center frequently discuss the use of EPO in the newborn HS population (9–12). The objective of this retrospective review was to evaluate the frequency and cost of EPO versus transfusion therapy in infants with HS at a single large pediatric hematology program.

Patients and Methods

Patient Identification

All patients diagnosed with HS (by family history, blood smear, laboratory parameters, and/or osmotic fragility test), born between July 2000 and June 2011, and followed by the hematology clinic at Boston Children's Hospital were eligible for this chart review. The 59 subjects with HS were identified from hematology department records and from an electronic clinic note search tool. Demographic, laboratory, and treatment data was collected through a retrospective chart review.

Survey

All clinical hematologists at Boston Children's Hospital received an invitation in 2011 to participate in an anonymous web-based survey regarding their use of EPO in infants with HS with a 67% response rate (32/48). The surveyed clinical hematologists were overlapping but not the same as the clinical hematologists from the 11-year study period. The study protocol was approved by the Institutional Review Board at Boston Children's Hospital.

Statistical Analysis

Study data were collected and managed using REDCap electronic data capture tools developed by Vanderbilt University and hosted at Boston Children's Hospital (13). Initial analysis compared the subset of patients who received EPO with those who did not, using Chi-Squared tests. Data were analyzed using SAS 9.2. All p-values are two-sided, and no adjustments were made for multiple comparisons.

Results

We identified 59 infants with HS born between July 2000 and June 2011 and followed in the hematology clinic at Boston Children's Hospital. 15% (9/59) of patients in this HS infant cohort received pharmacologic treatment with Epoetin alpha, and none received long-acting erythropoiesis-stimulating agents. EPO was prescribed at a mean age of 5.3 weeks (± 3.6 weeks). The mean EPO dose was 600 IU/kg/week (range: 200–1000 IU/kg/week) with three times per week dosing most commonly prescribed. Table 1 compares the characteristics of

these patients with those who were not treated with EPO. In general, patients treated with EPO were not different in terms of gestational age, birth weight, family history of HS, or history of neonatal jaundice.

Of the 9 infants treated with EPO, 6 (67%) had an older sibling with HS, of whom 3 were also treated with EPO. The average age at first visit for EPO-treated patients was 8.9 weeks and 16.1 weeks for patients who did not receive EPO ($p=0.1$). The mean nadir hemoglobin and number of transfusions in the first year of life were not statistically different in the EPO vs. non-EPO group (nadir hemoglobin: 7.6 vs. 8.1 g/dl, $p = 0.2$; number of transfusions: 0.9 vs. 1.1, $p=0.5$). However, 6/9 (67%) EPO-treated patients received a red blood cell transfusion prior to starting EPO therapy, and, of these, all were known to have HS pre-transfusion. EPO therapy was discontinued at a mean age of 23.5 weeks (range: 12–37 weeks). In total, 26/59 (44%) of patients in the study were transfused at least once in their first year of life. Common reasons for transfusion included symptomatic anemia (58%) and low hemoglobin levels without symptoms (34%).

In our academic center of more than 30 clinical hematologists, two clinicians commenced EPO therapy for over half of the treated infants at our center. To assess clinicians' views of the uses of EPO therapy in infants with HS, a survey was completed by 32 practicing hematologists at Boston Children's Hospital (Table 2). Of these clinicians, 60% believed EPO therapy to be a "somewhat" or "very effective" treatment for infants with HS, while only 31% had prescribed the treatment themselves. Given the identical clinical scenario on the survey of a typical 2 month old infant with HS presenting in clinic for the first time, hematologists at our center gave discrepant plans for management (Table 2).

The cost of EPO was calculated by using the average wholesale price (AWP) of the average dose of EPO (600 IU/kg/week), the average time period of administration (23.5 weeks), and 3-times-weekly injections at the infants' primary care office. The AWP of EPO is \$40.50 for every 3000 units. For an average sized infant of 5 kg, the total cost of a course of EPO is \$952 for the drug. The charge for an injection at Children's Hospital Primary Care Center is \$65, which totals \$4,583 for the course of treatment. Thus, the total cost of EPO treatment is estimated to be \$5,534 per infant. The \$1,783 charge for a red blood cell transfusion at the Children's Hospital Center for Ambulatory Treatment includes: \$373 per red cell unit, \$252 for IV placement, and \$1158 for monitoring the approximately four hour transfusion. Thus, the estimated cost of treatment with EPO is greater than the cost of two red cell transfusions.

Discussion

Various strategies exist to address the exaggerated anemia of infancy in patients with HS, including observation, red cell transfusions, and EPO therapy. Of the infants with HS followed at our center over the past 10 years, 44% received a red cell transfusion as support through their exaggerated physiologic nadir and 15% of infants received EPO. The majority of infants required a red cell transfusion prior to starting EPO.

Although an initial prospective study suggested that EPO may be beneficial in avoiding red cell transfusions in this population, that study was small, non-randomized, confused by

previously transfused neonates (as in our own series), and demonstrated that EPO had markedly variable results in different patients (5). Without a randomized study of supportive care versus EPO therapy in this patient population, the efficacy of EPO to avoid transfusion is unclear. Furthermore, the logistics of prescribing EPO therapy in this patient population, including the necessity of prior insurance authorization, three times weekly injection at the pediatrician's office, and cost are significant barriers to implementation of this therapy. Clinicians and families must weigh these logistics against the benefits of avoiding a red cell transfusion in the modern era of thorough screening of the blood supply.

With this mixed literature and the added logistical issues of administration of EPO in this population, we obtained discrepant results surveyed from clinicians at our center in terms of their approach to this patient population. Although the survey reflects variable levels of clinical experience and modern practice, the results also reflect the issue that the standard for managing this population in the neonatal period is not clear. Without proper evidence, as in many areas of medicine, unique practice customs and treatment strategies are implemented.

A larger, randomized prospective study would allow physicians to better make choices about the use of EPO in infants with HS and other hemolytic anemias. Given the costs and logistic issues of administering EPO to this patient population and the lack of evidence of clear benefit, supportive care may be a more sensible treatment choice. Until a definitive study establishes best practice, hematologists will continue to make individual choices, as seen by the variability in treatment plans for an identical clinical scenario at our center.

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Figure 1.

Hemoglobin in infants with hereditary spherocytosis (HS) vary by treatment strategy. Areas shaded in gray indicate normal range. Infants with HS have a markedly lower hemoglobin nadir in the first 3 months of life in comparison to healthy infants. Various approaches to this exaggerated anemia exist including A) no treatment (observation only), B) packed red cell transfusion, and C) Erythropoietin therapy (EPO). The patient in graph C did not respond to the first round of EPO therapy with doses at 700 u/kg/week, however did respond

after the dose was raised to 1000 u/kg/week. EPO therapy was later discontinued. Date of transfusion is marked on graph B with a "T".

Table 1

Comparison of the Clinical and Laboratory Characteristics of 59 Infants with Hereditary Spherocytosis (HS) by whether Patients were Treated with Erythropoietin (EPO)

	EPO n=9	No EPO n=50	p
Male	7 (77.8%)	32 (64%)	0.70
Gestational Age (weeks)	38.3	38.1	0.80
Birth Weight (kg)	3.5	3.3	0.71
Family History of HS	9 (100%)	44 (89.8%)	1
Neonatal Jaundice	8 (88.9%)	35 (74.5%)	0.67
Mean nadir hemoglobin *	7.6 (range 6.5–8.9)	8.1 (range 5.2–12.4)	0.39
Number of Transfusions **	0.9 (0–2)	1.1 (0–10)	0.29
HS Severity			0.09
Mild	1 (12.5%)	18 (38.6%)	
Moderate	7 (87.5%)	21 (50%)	
Severe	0 (0%)	7 (11.4%)	

* in the first 6 months of life

** in the first year of life

Table 2

Survey of 32 Pediatric Hematologists at a Single Center on the use of Erythropoietin (EPO) in Infants with Hereditary Spherocytosis (HS)

Level of Experience	
Fellows	12
Attending, Years 1–5 and NPs/PAs	11
Attending, Years >5	9
Mean Number of Infants with HS Clinician has followed	6 (range: 0–50)
Mean Number of HS Patients Clinician treated with EPO	0.66 (range: 0–5)
Number who report prescribing EPO to infants with HS	10
Percent Believe EPO to be somewhat or very effective for this indication	60%
Responses obtained from the following clinical scenario: “2 month old with a family history of HS is at clinic for a first visit and has severe anemia with normal growth. How would you manage this patient?”	40% Transfuse now, then expectant transfusions 20% Transfuse now, then EPO 20% Start EPO, no transfusion 20% I don't know