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Review article

The effects of recombinant human erythropoietin on growth and nutritional status

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Abstract. The availability of recombinant human erythropoietin (rhuEPO) has dramatically improved the care of children with chronic renal failure (CRF). Its use provides the opportunity to determine the relative contribution of anemia to the morbidity of CRF. Growth retardation, one of the most significant complications of CRF in children, is the consequence of several inter-related processes, including decreased protein and energy intake, metabolic bone disease, endocrine abnormalities, and anemia. The literature on the use of rhuEPO in children and data from a United States phase III double-blind, placebo-controlled study of rhuEPO in pediatric dialysis patients are reviewed to determine the effect of rhuEPO treatment on the nutritional status and growth of children with CRF. Despite subjective increases in appetite, there were no consistent improvements in dietary intake or anthropometric measures observed during rhuEPO treatment. Children gained weight during rhuEPO treatment; however, this was not generally associated with increased weight standard deviation scores. There was an improvement in growth velocity in some children; however, improvements in height standard deviation scores were infrequently seen. On review of the available literature, correction of anemia with rhuEPO has not been shown to improve the growth of children with CRF.

Key words: Growth – Nutrition – Erythropoietin – Hemodialysis – Peritoneal dialysis

Potential role of anemia in the growth failure of children with chronic renal failure

Most children with chronic renal failure (CRF) develop a normochromic, normocytic anemia by the time that their glomerular filtration rate has decreased to between 20 and 35 ml/min per 1.73 m^2 [1]. Insufficient renal erythropoietin synthesis is the primary cause of the anemia, with additional contributions from inhibition of erythropoiesis, decreased erythrocyte survival, and blood loss. Recombinant human erythropoietin (rhuEPO) overcomes these factors, ameliorates the anemia, and eliminates the need for blood transfusions in most patients [2]. In addition to dramatically improving the care of children with CRF, the availability of rhuEPO provides the opportunity to determine the relative contribution of anemia to the morbidity of CRF.

Multiple factors are thought to limit growth in children with CRF, including decreased protein and energy intake, metabolic bone disease, endocrine abnormalities, and anemia [3–5]. The endocrine abnormalities, which are reviewed elsewhere in this symposium, include alterations in the growth hormone/insulin-like growth factor (IGF) axis [6, 7]. The contribution of each of these factors is likely to vary among children of different ages and those with different primary renal diseases. In addition, these abnormalities are not independent, as anemia may contribute to anorexia and the resultant inadequate nutrition. Malnutrition may contribute to the endocrine alterations of CRF. As no one growth-inhibiting factor is present in isolation, the relative contribution of each to growth retardation cannot readily be determined.

In order to determine the role of anemia in growth failure, a review of the growth patterns of children with non-renal causes of anemia may be applicable. Children with sickle cell disease and thalassemia have inadequate growth [8, 9]. Specialized growth charts have been developed for children with sickle cell anemia. In addition, improved growth has been shown in children with thalassemia treated with hypertransfusion protocols [9]. The improvement is thought to be due to elimination of the increased energy demands for marrow activity and cardiovascular compensation for anemia.

The initial trials of rhuEPO in adults described improvements in appetite, so potential improvements in nutritional status and growth were anticipated in children [2]. It had been anticipated that children would feel better and have increased dietary intake resulting in improved growth. Improved nutrition might also improve the depressed bioactivity of IGF-I seen in these children. Prior to the

Table 1. Effects of recombinant human erythropoietin (rhuEPO) correction of anemia on nutrition

Report	Patient number/ treatment	Appetite	Dietary energy intake	Dietary protein intake	Midarm circumference	Triceps skin fold thickness
Campos and Garin [13]	11H	+			+	+
Morris et al. [18]	1H / 9P / 1C	+/–	–	–	–	–
Navarro et al. [14]	5H / 7P / 11C	+				
Scigalla et al. [19]	43H / 8P	+/–				
Sinai-Trieman et al. [15]	5P	+				
Stefanidis et al. [17]	10P	+	–	–	–	–
Warady et al. [16]	9P	+	–	–		
U. S. multicenter trial	24H / 38P		–	–		

H, Hemodialysis; P, peritoneal dialysis; C, conservative treatment prior to dialysis; +, improvement or increase during rhuEPO treatment; –, no change during rhuEPO treatment; +/–, improvement in some children; an empty space indicates that the variable was not assessed in the report

introduction of rhuEPO, it was reasonable to speculate that the amelioration of anemia would improve growth directly through improved tissue oxygenation or indirectly through improved nutrition. Now that there are several years of experience with rhuEPO we can answer the question: "does the correction of anemia with erythropoietin improve growth in uremic children?"

This review will look at the current evidence for an effect of correction of anemia on appetite, dietary intake, nutritional status, weight gain, and growth. The data assessed are derived from trials of rhuEPO in children, including results of the United States multicenter trial of rhuEPO in pediatric dialysis patients [10, 11].

Overview of United States multicenter trial of rhuEPO in pediatric dialysis patients

This controlled trial of rhuEPO in pediatric hemodialysis and peritoneal dialysis patients was conducted from October 1990 to September 1993 with the primary goal of determining the safety and efficacy of rhuEPO in children. The study included 113 children at 15 United States sites who were randomized for a 12-week study period to rhuEPO or placebo. Prior to starting rhuEPO treatment, the mean hematocrit (Hct) in those on hemodialysis was 21% and those on peritoneal dialysis 22%. After the 12-week placebo-controlled period all patients received rhuEPO. After 24 and 36 weeks of rhuEPO the mean Hct in both the hemodialysis and peritoneal dialysis patients was 31% [10]. The data to be reviewed include 3-day dietary histories and growth data collected every 12 weeks throughout the study. The patient diaries were reviewed centrally by a registered dietitian and entered into Computrition, a software program for calculation of nutritional parameters. The dietary intake was compared to the recommended dietary allowances (RDA) based on chronological age (Recommended Dietary Allowances, 10th edition, 1989). Standardized height and weight scores (SDS) were computed using the means and standard deviations of height and weight for age and sex for normal subjects published by the National Center for Health Statistics [12]. Paired *t*-tests were used to determine the differences between dietary intakes, weights, and heights at baseline and during rhuEPO treatment. The number of patients with complete data for each analysis varies.

Effect of correction of anemia on appetite and dietary intake

On the basis of early adult trials an increase in appetite was anticipated [2]. The reports of pediatric trials that assessed appetite changes during rhuEPO treatment are listed in Table 1. In the reports by Campos and Garin [13], Navarro et al. [14], Sinai-Trieman et al. [15], Warady et al. [16], and Stefanidis et al. [17] there was a subjective increase in appetite in all patients. The change in appetite was assessed using serial questionnaires in other studies [18, 19]. Morris et al. [18] noted a marked increase in appetite in some children, which was reversed during a cross-over to placebo treatment. In the 1989 report of a European multicenter trial, 37% of the patients had increased appetites [19].

Table 2. Effects of rhuEPO correction of anemia on growth

Report	Patient number/ treatment	Weight gain	Weight SDS	Growth velocity	Height SDS
Morris et al. [18]	1H / 9P / 1C		+/–		
Navarro et al. [14]	5H / 7P / 11C	+			–
Offner et al. [22]	14P	+	–	–	
Rees et al. [24]	6H			+/–	
Schärer et al. [25]	11C	+	–		+/–
Scigalla et al. [19]	43H / 8P	+			
Schaefer et al. [23]	108H / 12P			+/–	+/–
Stefanidis et al. [17]	10P			–	
U. S. multicenter trial [11]	32H / 49P		–		–

SDS, Standard deviation score

Despite increases in appetite, consistent increases in the dietary intake of calories or protein have not been observed. Morris et al. [18] collected 3-day dietary histories every 12 weeks and found an increase in energy intake in some children without a significant increase in the mean intake for the group. There was no increase in protein intake. There was no improvement in intake in the reports of Warady et al. [16] and Stefanidis et al. [17]. Of note, in the study of Stefanidis et al. [17] there was no evidence of malnutrition at the start of rhuEPO treatment [17]. It was suggested that "normal" intakes for age would not be increased with rhuEPO treatment.

Analysis of dietary intake in the United States trial showed similar results. The baseline caloric intake was 65% ± 4% of the RDA (mean, SE) and the protein intake was 120% ± 8% of the RDA. During rhuEPO treatment there was no significant change in the caloric (73% ± 4% of RDA) intake, although the protein (140% ± 9% of RDA) intake increased ($p = 0.04$). There was no difference in the baseline intakes or the effect of rhuEPO treatment between those on peritoneal dialysis and those on hemodialysis. There was a non-significant trend to a greater increase in energy intake for those with the lowest baseline intakes.

Estimation of nutritional intake with dietary diaries may be inaccurate, because the data are collected from multiple observers and are often incomplete and imprecise. Another approach is the measurement of the protein catabolic rate (PCR). Serial PCR measures were obtained in stable pediatric hemodialysis patients receiving rhuEPO [20, 21]. The PCR increased in some patients during rhuEPO treatment, suggesting increased protein intake.

The effect of correction of anemia on nutritional status has also been assessed through anthropometric measures. There are three reports of serial anthropometric measures during rhuEPO treatment (Table 1) [13, 17, 18]. The midarm circumference is a measure of lean body mass and the triceps skin fold thickness is used to assess body fat. In one study of 11 hemodialysis patients, a 5% increase in midarm circumference was noted with a 15% increase in triceps skin fold thickness after 3 months [13]. There was no further improvement subsequent to that. Morris et al. [18] found a non-significant increase in midarm circumference without a change in triceps skin fold thickness; Stefanidis et al. [17] reported no change in either parameter.

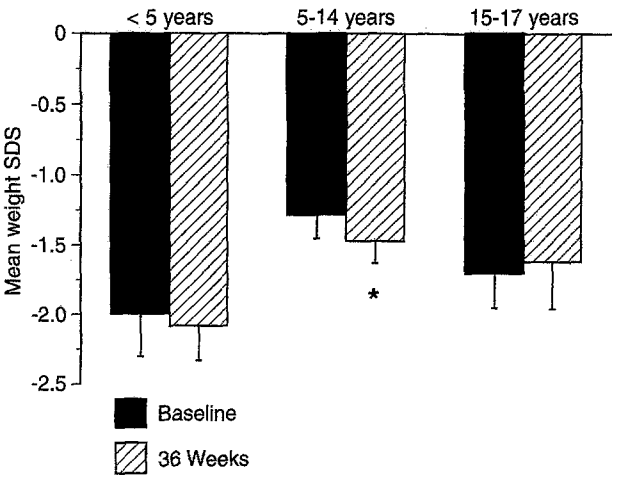

Fig. 1. Mean weight standard deviation scores (*SDS*) at baseline (*solid bars*) and after 36 weeks on recombinant human erythropoietin (rhuEPO) (*hatched bars*). In this analysis, there were 11 children < 5 years of age, 45 children 5–14 years, and 24 children 15–17 years. The standard errors are indicated. * $P < 0.02$ baseline vs. treatment

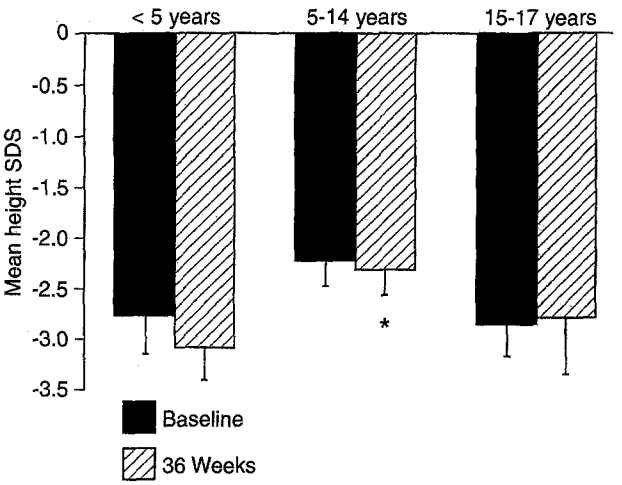

Fig. 2. Mean height SDS at baseline (*solid bars*) and after 36 weeks on rhuEPO (*hatched bars*). In this analysis, there were 11 children < 5 years of age, 45 children 5–14 years, and 24 children 15–17 years. The standard errors are indicated. * $P < 0.03$ baseline vs. treatment

Effect of correction of anemia on weight gain

Assessments of changes in weight have included measures of absolute weight gain as well as changes in weight SDS (Table 2). There was a significant weight gain during rhuEPO treatment each time it was assessed [14, 19, 22, 23]. In most reports there was no change in the weight SDS. However, Morris et al. [18] found an increase in weight SDS in some children without a significant increase in the mean SDS. In the United States multicenter trial there was no change in the mean weight SDS over the 36-week treatment period (−1.5 ± 0.2 vs. −1.6 ± 0.1) [11]. There was no difference between children receiving hemodialysis and those on peritoneal dialysis. There was no improvement in weight SDS in any age group (Fig. 1).

Effect of correction of anemia on growth

Growth was measured as a change in the growth velocity or the height SDS (Table 2). There was an acceleration of growth in some children [23, 24]. In one report the growth velocity was slightly increased in three prepubertal children 4–8 years of age without a change in three pubertal children [24]. In 11 children receiving conservative treatment there was a significant increase in SDS in 2 infants, without any change in 4 children 1–12 years of age [25]. In the European multicenter trial, there were improvements noted in some children without a significant change in the mean SDS [23].

Similarly, in the United States trial, there was a marked increase in height in some children without a change in the

height SDS (Fig. 2) [11]. There was no correlation between the baseline energy intake or the severity of baseline anemia and changes in height or weight SDS. None of these children was receiving growth hormone.

In summary, a review of currently available data shows that despite subjective increases in appetite, no consistent improvement in dietary intake or anthropometric measures has been observed during rhuEPO treatment in children. Children gained weight during rhuEPO treatment; however, there was no consistent increase in weight SDS. There was an improvement in growth velocity in some children; however, improvement in height SDS was infrequently seen. Correction of anemia with rhuEPO has not been shown to improve the growth of children with CRF.

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