Recombinant Human Erythropoietin for the Treatment of Anemia in Children With Solid Malignant Tumors

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Background
Cancer is often associated with chronic anemia which frequently requires blood transfusions. This study was performed to assess the efficacy and safety of r-HuEPO therapy in children with cancer.

Patients and methods
Twenty-five patients under 18 years of age with solid malignant tumors were treated with 150 U/kg/day of r-HuEPO 5 times weekly for 12 weeks. Response was defined as an increase of the baseline hemoglobin level by at least 2 g/dl. r-HuEPO patients were compared to 25 matched historical controls.

Results
Response was achieved in 72% of r-HuEPO patients. Hemoglobin level increased from 9.8 ± 0.6 g/dl at baseline to 12.4 ± 1.7 g/dl at the end of treatment in the r-HuEPO group and increased from 9.5 ± 0.7 g/dl to 9.6 ± 1.4 g/dl in the control group ($P < .001$, Student's t-test). Only 16% of patients receiving r-HuEPO required blood transfusions vs 96% of control patients ($P < .001$, Student's t-test), with mean units of blood transfused per patient being 0.35 in the r-HuEPO group and 3.56 in controls ($P < .001$, Student's t-test). There was a statistically significance improvement in Karnofsky's index in r-HuEPO patients. No adverse reaction related to r-HuEPO therapy was observed.

Conclusions
r-HuEPO is a safe and effective means of increasing hemoglobin level and reducing blood requirements in children with solid malignant tumors receiving chemotherapy.

Key words
Recombinant human erythropoietin; anemia, cancer; chemotherapy; children.

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INTRODUCTION

Anemia is commonly observed in cancer patients before any myelosuppressive therapy is administered, and may be multifactorial in origin [1]. Nutritional deficiencies, chemotherapy, radiation, bone marrow infiltration, hemorrhages, sequestration in an enlarged spleen, or hemolysis may cause anemia [2], but anemia of chronic disease probably plays the fundamental role in most anemic cancer patients [3,4] with an inadequate erythropoietin (EPO) response to the degree of anemia [5].

Cancer patients with symptoms of anemia frequently require red cell transfusions [6], which carry significant risks in up to 20% of cases [7–10]. Since recombinant human erythropoietin (r-HuEPO) became available, it has been safely and successfully used in anemic patients with renal disease [11], in AIDS patients treated with zidovudine [12], after bone marrow transplantation [13], for rheumatoid arthritis [14], and for chemotherapy-induced anemia in adult cancer patients [15,16]. We report a pilot study to evaluate the clinical utility of r-HuEPO as an alternative to blood transfusion for anemia in pediatric cancer patients receiving chemotherapy.

PATIENTS AND METHODS

The trial was an open-label, single-institution, pilot study of safety and efficacy. The protocol was approved by the Ethics Committee of our hospital and written informed consent was obtained from at least one parent or a legal representative of all patients.

Patients and Historical Controls

The study concerns patients under 18 years of age with a diagnosis of solid malignancy confirmed by biopsy specimen, who received cyclic combination chemotherapy for a total of at least 5 days every 3–4 weeks. Prior to study all patients had a life expectancy of at least 3 months, and had been clinically stable for at least 1 month. Laboratory values for inclusion were as follows: hemoglobin (Hb) concentration < 10.5 g/dl, absolute neutrophil count (ANC) > 0.5×10^3 cells/µl, platelet count >75×10^3 cells/µl, reticulocyte count < 3%, creatinine concentration < 2.0 mg/dl, serum calcium level < 12.0 mg/dl, serum folate, vitamin B_{12}, AST, ALT, bilirubin, and urine analysis within normal limits, ferritin > 30 ng/ml, transferrin saturation > 15%, negative Coombs' test and stool negative for occult blood. Exclusion criteria were: known cerebral metastases, uncontrolled hypertension, seizures, causes of anemia other than chronic neoplastic disease (such as folate and vitamin B12 deficiency, iron deficiency, gastrointestinal bleeding, hemolysis, ...), acute illness within 7 days of study entry, experimental therapy or surgical treatment within 30 days of study entry.

Patients were compared to matched historical controls. Protocols of chemotherapy were continued and unmodified during the study. Standard clinical practices and chemotherapy protocols were similar in both groups.

Treatment Regimen

The r-HuEPO was supplied by Boehringer Mannheim, Barcelona, Spain, and administered subcutaneously in a dose of 150 U/kg/day 5 times weekly for 12 consecutive weeks. Oral iron supplements were commenced if serum ferritin fell to <100 ng/ml and/or transferrin saturation fell to <20%.

Clinical and Laboratory Monitoring

Medical history and physical examination, a complete blood cell count, reticulocyte count, determinations of serum iron, ferritin, transferrin saturation, folate, vitamin B_{12}, electrolytes, glucose, ALT, AST, bilirubin, performance status according to Karnofsky's index [17], and blood transfusion information were recorded at baseline, every 3–4 weeks (chemotherapy cycle), and at the end of study. Baseline assessments also included 12-lead electrocardiogram, chest x-rays, urinalysis, test of stool for occult blood, and serum EPO level measured by radioimmunoassay (Diagnostic Systems Laboratories, Texas, USA). To define EPO levels as appropriate or inappropriate for a given degree of anemia, the observed/ predicted log (serum EPO) ratio (O/P ratio) was calculated [18]. The predictive value of EPO for a given degree of anemia was determined by a regression equation obtained by Beguin et al. [19] from reference subjects. During r-HuEPO therapy, weekly assessment of blood pressure and pulse and respiratory rates were performed.

Transfusion Practice and Intensity of Chemotherapy

Red cell transfusions were performed if Hb level fell to <9 g/dl and/or symptoms of anemia were developed. The transfusion trigger was determined in both r-HuEPO and control groups to ensure that results were not influenced by differential transfusion practice. The Hb threshold of 9 g/dl might be regarded as relatively high for blood transfusion. However, this trigger was chosen because ours is a reference department for Pediatric Oncology and most of the patients live far from the hospital with an average distance of 350 kilometers. Therefore, an urgent treatment of anemia cannot be undergone when patients are between hospitalization periods.

The intensity of chemotherapy was measured in order to account for the possible effects on our results of differences in intensity between the r-HuEPO and control group. Since the patients received a wide variety of different chemotherapy regimens, a surrogate marker for the intensity of chemotherapy was used. The most appropriate marker appeared to be the effect of chemotherapy on neutrophil and platelet counts. Therefore, the determinations included the number of episodes in which ANC fell to <1000 or <500 cells/ml and platelet count fell to <50000 or 20000 cells/ml (15).

Response Criteria

"Response" was defined as an increase of Hb of at least 2 g/dl with respect to the baseline level within 12 weeks without red cell transfusions [20,21].

Evaluation of Toxic Effects

Any abnormal vital signs or clinically significant abnormal laboratory findings were recorded for consideration as toxic effect.

Statistical Evaluation

Statistical inference for dichotomous variables formulated as 2 × 2 tables was carried out using Fischer's Exact Test. Analysis of variance was used to compare repetitive measurements. Two-sample *t*-tests were used to compare means between groups, and paired *t*-tests were used to test changes from baseline to other values. All statistical tests of hypotheses were two-sided and were carried out at the $\alpha = 0.05$ level.

RESULTS

Demographic and Baseline Characteristics

A total of 25 patients were enrolled into the study between February 1994 and May 1995 and received r-HuEPO therapy. All of them completed the 12 weeks of treatment. The historical control group included 25 patients treated in our department between September 1992 and January 1994. The demographic and baseline characteristics of both groups are listed in Table I. There were no statistically significant differences between groups for these data.

Hematologic Measurements

The kinetics of Hb levels are shown in Figure 1a. Baseline mean ± SD Hb level was similar (P = .80) in both groups: 9.8 ± 0.6 g/dl in r-HuEPO group and 9.5 ± 0.7 g/dl in controls. The Hb level of r-HuEPO group increased relative to the control group and this increase was statistically significant by week 6 (11.9 ± 2.2 vs. 10.4 ± 1.2 g/dl; P = .023), at week 9 (11.7 ± 2.1 vs. 10.2 ± 1.3 g/dl; P = .039) and at the end of therapy (12.4 ± 1.7 vs. 9.6 ± 1.4 g/dl; P < .001). No relationship was observed between Hb level and type of tumor nor the presence of bone marrow metastases. There were no statistically significant differences in response to r-HuEPO as a function of the severity of the anemia.

In the r-HuEPO group the median absolute reticulocyte count increased from 60000/µl (baseline value) to 126296/µl at week 6 (P = .011), 156185/µl at week 10 (P = .003), and 134678/µl at the end of study (P = .007). There were no significant differences between groups regarding mean corpuscular volume, mean corpuscular Hb, mean corpuscular Hb concentration, white blood count, and platelets.

Serum EPO Levels

Mean serum EPO level was 42.6 mU/ml (range: 7.8– 134.4) at baseline in the r-HuEPO group. Endogenous EPO production, measured by O/P ratio, was appropriate for the degree of anemia in only 3 patients (Table I). No data on EPO were available in the control group.

Intensity of Chemotherapy

Intensity of chemotherapy (as measured by neutrophil and platelet counts) for r-HuEPO and control patients was not significantly different ($P > .05$) (Table I).

Transfusion Requirements

The percentages of patients transfused before entry into the study were 80% in the r-HuEPO group and 84% in the control group (Figure 2a), the mean number of units of blood per patient being 2.3 (range: 0–10) and 2.5 (range: 0–7), respectively (Figure 2b). These differences at baseline were not statistically significant. During the study, the percentages of patients requiring blood transfusion were 16% (4 out of 25) in the r-HuEPO group and 96% (24 out of 25) in the control group (Figure 2a), the mean number of units of blood transfused per patient being 0.35 (range: 0–4) and 3.56 (range: 0–8), respectively (Figure 2b). These differences between the groups were statistically significant ($P < .001$). The mean Hb level at which patient were given transfusions was 8.8 g/dl in r-HuEPO group and 8.9 g/dl in controls ($P > .05$).

Response

In the r-HuEPO group, 18 patients responded by increases of at least 2 g/dl in Hb level, without requiring blood transfusion. Most responders achieved the necessary increase in Hb level between the fourth and eighth weeks of therapy.

Karnofsky's Index

The mean baseline values of Karnofsky's index were 70.8% in r-HuEPO group and 71.2% in controls ($P > .05$). In the r-HuEPO group there was a statistically significant improvement ($P < .05$) in Karnofsky's index between the start and the end of the study (Figure 1b). No such improvement was seen in the control group. Of the 15 r-HuEPO patients whose Karnofsky's index improved, 13 were responders and 2 were non-responders.

Iron Parameters

Serum ferritin level was high at baseline in the r-HuEPO group (probably due to pretransfusions) (307 ng/ ml; range: 25–1200). Changes in serum ferritin concentrations during the study fell to reach the limit of statistical significance at week 3 ($P = .028$) and

week 6 (P = .049), increasing after weeks 9 and 12, but with no statistical significance (P > .05). Transferrin saturation followed a parallel evolution during the study. Fourteen (56%) patients in r-HuEPO group required iron supple-mentation during a mean time of 7.2 weeks (range: 3– 12).

Safety

Treatment was well tolerated. No patient was removed from the study because of r-HuEPO-related toxicity. No severe adverse effect was reported.

Other Effects

No statistical differences between the groups regarding electrolytes, serum creatinine, glucose, bilirubin, AST, and ALT were observed.

DISCUSSION

Anemia is common in cancer patients and red blood cell transfusions are often required. Transfusions are still associated with some adverse reactions and another problem may be represented by religious beliefs. Although the mechanism of cancer-related anemia is not well known, it appears that an inadequated EPO response plays a fundamental role [5]. Recently, some studies have been performed using r-HuEPO to treat anemia in adult cancer patients [15,16,21,22]. To confirm and extend the outcome of these results, we performed this pilot study in pediatric cancer patients.

The present study demonstrates that r-HuEPO increases the Hb level in pediatric cancer patients receiving chemotherapy. The increase in Hb concentration from baseline to the end of study was greater in r-HuEPO treated patients than in controls. This result is in accordance with those reported in the literature [15,16,20–24]. However, in pediatric patients the published data is controversial. Nenadov Beck et al. [25] conclude that r-HuEPO administration was safe but ineffective, probably due to a mechanism of transient primary resistance. On the other hand, similar results to ours have been reported by Locatelli et al. [18] in children with acute leukemia given allogeneic bone marrow transplantation, and by Kronberger et al. [26] in pediatric patients with Ewing's sarcoma and osteosarcoma.

We did not observe any statistically significant correlation between increase in Hb levels and tumor type in our study, but this is not very indicative, given the limited number of cases of each tumor type and the fact that hematological malignancies were not included. Interestingly, neither tumor type nor bone marrow involvement appeared to influence the response to r-HuEPO therapy [27]. Patients with hematologic and solid tumors respond equally well to r-HuEPO [15].

r-HuEPO has been shown to promote both granulocyte and megakaryocyte colony growth [28,29]. In our study, as in others [18,22], there were no significant differences between the r-HuEPO group and control group in either white blood cell or platelet counts.

The transfusion history of the patients was almost identical in the r-HuEPO and control groups, but subsequent to the improvement in Hb levels in r-HuEPO treated patients there was a reduction in the transfusion requirements of this group. This reduction is consistent with the findings of other authors [16,18,21,30,31]. Abels [15] observes that transfusion rates were reduced after 1 month of r-HuEPO therapy, suggesting that this lag in response was probably related to the time required for the stimulation of erythropoiesis to be reflected in decreased transfusion practice.

Response was achieved in 72% of r-HuEPO patients. Tumor type and bone marrow involvement did not appear to influence the response rate. This response percentage is not associated with differential transfusion practice between groups, nor with a differential intensity of chemotherapy. The response rates in published studies are in accordance with our findings, and range from 31.7% [15] to 82–85% [16,32], reflecting differences in dose, route of administration, duration of therapy, the response criteria used, and the patient population under study [27].

Although most patients in this study had a favorable Karnofsky's index at baseline, the r-HuEPO patients achieved a statistically significant improvement of their scores from the third week of treatment. This observed improvement is in accordance with reports on the effect of r-HuEPO therapy in patients with end-stage renal disease [33], and in adult cancer patients [15,21,31,34]. Improvements in quality of life of patients with response to therapy may be explained by the clinically observable subsiding of all or most symptoms of anemia [34]. Even two patients with no response to r-HuEPO treatment had some significant improvement during therapy, as reported by Leitgeb et al. [34] and Ludwig et al. [21], probably due to placebo effect or marginal beneficial effects of the treatment.

In accordance with other reports [16,21,25], r-HuEPO treatment was excellently tolerated by all patients, causing no severe adverse reaction. No patient complained of the local burning sensation at the site of injection primarily related to epoetin-α administration. Although hypertension in cancer patients receiving r-HuEPO has been reported [22], it is less frequent and of easier management than in renal patients [11].

CONCLUSIONS

This study demonstrates that r-HuEPO therapy is a safe and effective means of increasing Hb level and reducing blood requirements in pediatric patients with malignant solid tumors receiving chemotherapy.

On the basis of this data, we suggest that more extensive trials in pediatric cancer patients should be embarked upon in order to clarify the effect on transfusion requirements, to define the optimal dose and to identify prediction factors for response to r-HuEPO therapy.

ACKNOWLEDGMENTS

We thank Xavier Llobet, MD, and Antonio Mayol, MD, from Boehringer Mannheim, Barcelona, for providing us the r-HuEPO and support for the study and to David Burdon for the grammar revision of the manuscript.

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Table 1. Demographic and Baseline Characteristics

Parameter	**r-HuEPO***	**Control***
Number of patients	25	25
Sex		
Male	14	14
Female	11	11
Mean age, y (range)	12.6 (6–17)	11.8 (5–17)
Mean ± SD weight (kg)	49.4 ± 16.1	44.3 ± 16.6
Mean ± SD height (cm)	156 ± 16.1	148.8 ± 19.6
Mean ± SD Hb level (g/dl)	9.8 ± 0.6	9.5 ± 0.7
Mean ± SD WBC count (×µl)	5904 ± 3170	7517 ± 3080
Mean ± SD platelet count (×µl)	256000 ± 72000	254000 ± 69000
Mean serum EPO, mU/ml (range)	42.6 (7.8–134.4)	□□
Mean O/P ratio (range)	0.7 (0.44–1.08)	□□
O/P ratio <1 (% of patients)	88	□□
Tumor type (%)		
Ewing's sarcoma	36	40
Ostesarcoma	32	32
CNS tumors	16	16
Hodgkin's lymphoma	8	8
Rhabdomyosarcoma	4	4
Unknown primary site	4	□□
N of episodes with ANC <1000 cells/µl	14	12
N of episodes with ANC <500 cells/µl	20	18
N of episodes with platelets <50000/µl	11	7
N of episodes with platelets <20000/µl	4	5

*No statistically significant differences ($P > .05$) between groups.
y: years; Hb; hemoglobin; WBC: white blood cell; CNS: central nervous system; O/P ratio: observed/predicted log (serum EPO) ratio; N: number of data; ANC: absolute neutrophil count.

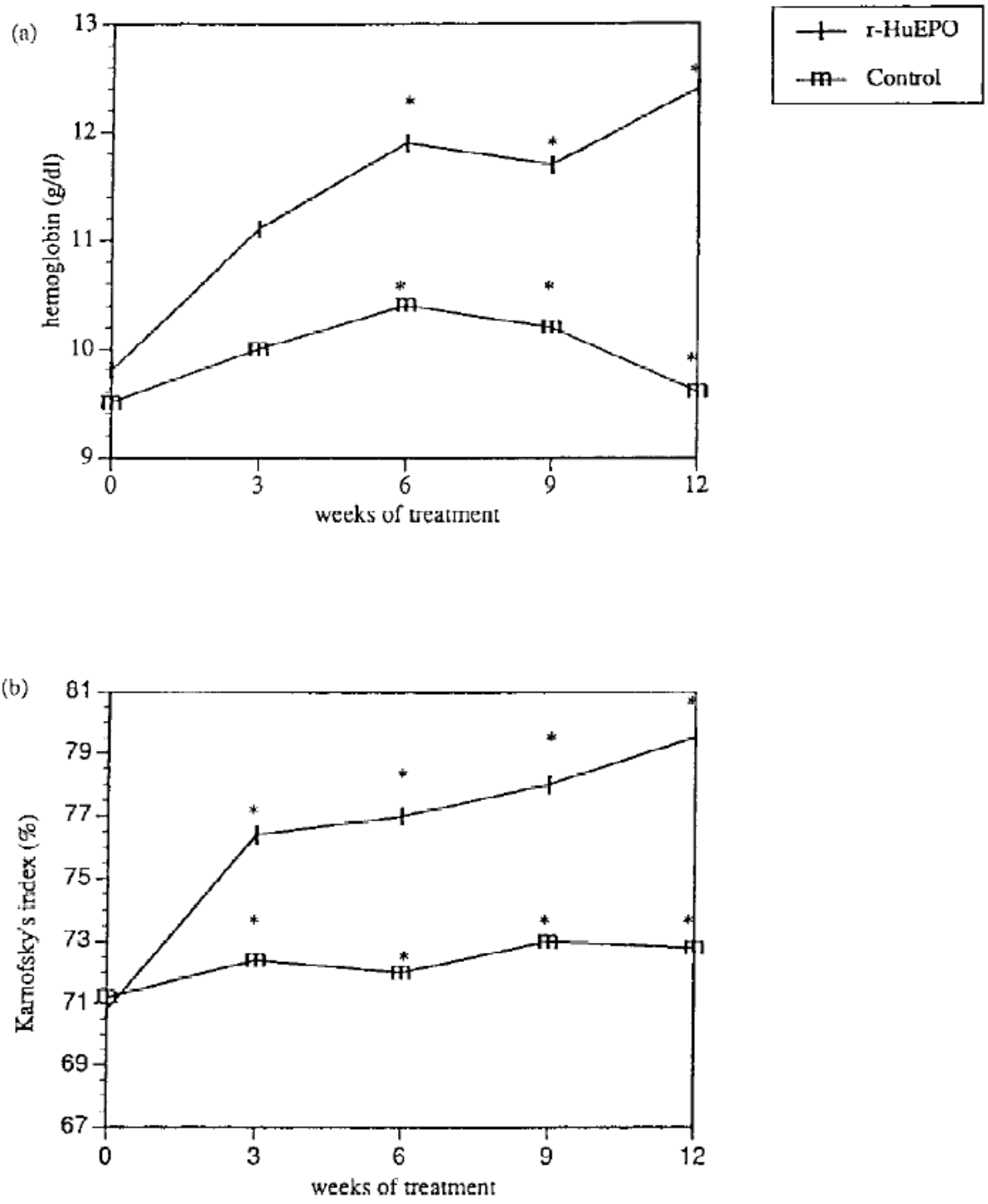

Figure 1. Changes in hemoglobin levels (a) and Karnofsky's index (b) in both groups during study. *$P < .05$, Student's *t*-test.

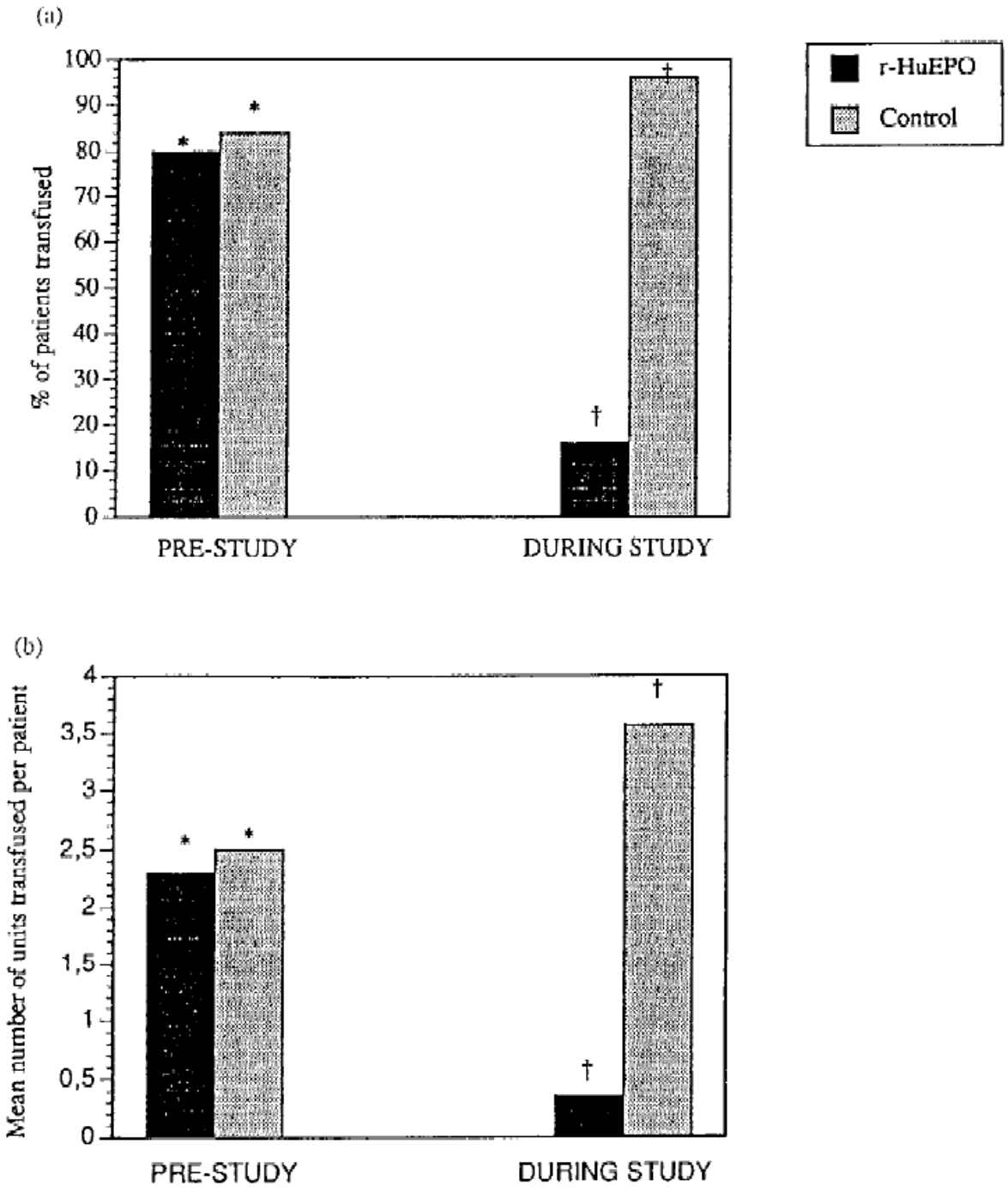

Figure 2. Percentage of patients (a) and mean number of units transfused per patient (b) before (left columns) and during (right columns) study period. *$P > .05$; †$P < .001$, Student's *t*-test.