Autologous blood transfusion with recombinant erythropoietin treatment

22 arthroplasties for rheumatoid arthritis

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12 anemic and 10 non-anemic patients with rheumatoid arthritis were treated with recombinant human erythropoietin (rHuEPO) before arthroplasty. The patients received 400–800 units/kg of rHuEPO subcutaneously once a week. Autologous blood was collected after the hemoglobin concentration was increased by 5 percent or more. All but one of the patients responded to the treatment. They were given 1–3 units of autologous blood, and underwent the operation without homologous blood transfusion. The mean duration of the treatment was 1 month. In 1 patient with severe anemia, additional transfusion with 2 units of blood was necessary during the operation. In all patients, there was a tendency for the hemoglobin response ratio to rHuEPO to correlate negatively with the initial CRP levels. The treatment did not affect the patients' clinical rheumatologic condition and there were no adverse effects. These results demonstrated that the treatment with subcutaneous rHuEPO is both effective and non-toxic and can therefore eliminate the need for homologous blood transfusion in anemic patients undergoing arthroplasty for rheumatoid arthritis.

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Recombinant human erythropoietin (rHuEPO) has proved to be effective in treating anemia in patients with renal insufficiency (Eschbach et al. 1987), and the clinical use of rHuEPO in anemic patients with rheumatoid arthritis (RA) has also been reported (Means et al. 1989).

Although autologous blood donation with rHuEPO before elective orthopedic surgery has been widely endorsed as a good transfusion practice (Levine et al. 1988, Goodnough et al. 1989, Maeda et al. 1989), such procedures have not been reported in patients with RA who have anemia with the characteristics of chronic inflammatory disease. In fact, the majority of anemic patients with RA require a homologous blood transfusion in association with joint replacement surgery.

The purpose of this study was not only to evaluate the effect of subcutaneous rHuEPO injection in patients with RA but also to determine whether the need for homologous blood transfusions could be reduced or eliminated in patients undergoing arthroplasty.

Patients and methods

12 anemic patients (all women) and 10 non-anemic patients (2 men, 8 women) with RA, according to the 1987 revised criteria of the American Rheumatism Association (Arnett et al. 1988), were examined. Informed consent was obtained, and the study was approved by our University Committee of Medical Ethics.

All patients were scheduled to undergo either total hip arthroplasty (THA) or total knee arthroplasty (TKA) in our hospital between March 1991 and July 1992. The mean age of the patients was 58 (40–75) years. The mean duration of disease was 15 (1–40) years. 19 patients were seropositive for RA (Table 1). 11 patients were treated with disease-modifying antirheumatic drugs (7 patients bucillamine, 2 patients D-penicillamine, 1 patient auranofin). 12 patients were systemically treated with various doses of prednisolone. 2 patients (Nos. 15 and 18) had been orally treated with 2.5 mg/week of methotrexate. None of them had any kidney, lung or heart disease. All the patients had signs of active inflammatory disease with increased erythrocyte sedimentation rate, CRP level and a high Ritchie index.

Table 1. Patient characteristics

A	B	C	D	E	F	G	H	I
1	52	F	42	1	19	IV	3	21
2	58	F	55	9	260	IV	3	10
3	65	F	49	7	42	IV	4	7
4	69	F	35	10	79	IV	3	11
5	45	F	36	3	163	IV	3	14
6	40	F	48	20	199	IV	2	14
7	43	M	61	12	333	IV	2	10
8	52	F	46	10	97	III	3	11
9	75	F	59	11	20	III	3	12
10	43	F	38	19	291	IV	4	8
11	66	F	38	12	149	IV	4	16
12	60	M	48	27	24	IV	3	8
13	62	F	34	40	6218	IV	3	13
14	63	F	40	26	93	IV	3	25
15	57	F	42	13	1422	IV	3	6
16	57	F	58	16	23	III	3	10
17	61	F	71	6	165	III	3	8
18	66	F	65	8	91	III	3	10
19	60	F	43	16	251	III	3	28
20	68	F	68	17	172	III	3	31
21	49	F	43	25	21	III	3	10
22	58	F	32	11	219	IV	3	15
Mean	58		48	15	471			14

A Patient no.
B Age
C Sex
D Body weight, kg
E Disease duration, years
F Rheumatoid factor (units/mL)
G Radiographic stage 0–4 was assigned to the most severely damaged joint according to Steinbrocker et al. (1949)
H Functional class I–IV was assigned to the patient's functional impairment, according to Steinbrocker et al. (1949)
I Ritchie index was assessed by numerical measurement of joint tenderness according to Ritchie et al. (1968). The maximum possible score is 78

Administration of recombinant human erythropoietin and iron sulfate

All the patients received rHuEPO (Kirin Brewery Co, Ltd, Tokyo and Sankyo Pharmaceutical Co, Ltd, Tokyo) in an initial dose of 400 or 600 units/kg body weight subcutaneously once a week. In the patients with a low response to rHuEPO, the dosage was then increased to 600 or 800 units/kg. The treatment was continued until an appropriate volume of autologous blood was collected. The mean total dose of rHuEPO was 3170 (1200–6600) units/kg (Table 2). All patients received oral ferrous sulfate 200 mg per day throughout the treatment.

Autologous blood

The hemoglobin concentration was measured prior to each donation and if it had a level of 105 percent or more, as compared with the initial hemoglobin concentration, blood was collected. Since the degree to which the hemoglobin concentration increases differs considerably among the patients, the donation schedule was different among them. The patients had to be in good health, with a normal blood pressure and body temperature at the time of each donation. Each single donation was 1 unit, which equals about 400 g, and donation was performed either 2 or 3 times during rHuEPO treatment. Blood cells were stored in a mannitol-adenine-phosphate solution (Japanese Red Cross Institution) at 1–6 °C. With this solution, blood cells can be stored in a liquid state for as long as 6 weeks. Fresh-frozen plasma was made from whole blood units within 1 hour of collection and then frozen. The operation was scheduled within at least 1 week after the last donation to allow for the recovery of the hemoglobin level.

Surgical procedures and autologous blood reinfusion

12 patients had 12 cemented THA, using the Harris precoat hip system, and 10 patients had 11 cemented TKA using the KINEMAX modular total knee system, including 1 case of bilateral TKA. In TKA, a tourniquet was used throughout the operation in all cases. The whole collected autologous blood was reinfused to each patient either intraoperatively or within 48 hours postoperatively.

Clinical and laboratory evaluation

For a rheumatological clinical evaluation, the Ritchie articular index (Ritchie et al. 1968) and the Steinbrocker functional class (Steinbrocker et al. 1949) were evaluated every week. All the patients underwent regular check-ups for routine hematology, serum chemistry, the reticulocyte count, as well as the measurement of serum ferritin and iron. The serum erythropoietin levels were measured before the day of the first rHuEPO injection, by a radioimmunoassay, using radiolabeled recombinant human erythropoietin as the antigen and monoclonal antibody to human erythropoietin (Kanao et al. 1989). The sensitivity of this method was 3 μunits/mL and the coefficient of variation was within 5.5 percent.

Assessment of the hemoglobin response ratio to rHuEPO

The estimated hemoglobin increase and the hemoglobin response ratio to rHuEPO in the patients were calculated as shown below:

The estimated hemoglobin increase (g/dL) = Hemoglobin concentration after the treatment (g/dL)–Initial hemoglobin concentration (g/dL) + Σ (hemoglobin concentration just before donation (g/dL) × Collected blood volume (L) / 0.06 × body weight(kg)).

Table 2. Treatment with rHuEPO, volume of autologous blood, operative blood loss and changes in hemoglobin concentration

A	B	C	D	E	F	G	H	I
1	RH	62	3400	3	935	7.4	11.2	9.6
2	RH	35	2600	3	630	11.8	8.9	10.0
3	LH	41	3600	3	950	12.3	12.3	12.6
4	LH	41	4200	3	880	9.3	9.2	9.3
5	RH	42	4800	3	870	13.7	12.5	12.2
6	LH	59	4800	3	1405	9.5	10.7	9.2
7	RH	36	2000	2	1150	11.7	10.2	10.6
8	RH	45	3200	2	1855	10.7	11.1	8.0
9	LH	46	1600	2	1200	13.1	13.4	11.1
10	RH	29	1800	3	1835	11.7	9.6	9.0
11	RH	56	5600	3	720	10.3	12.1	13.3
12	LH	57	3600	2	1585	12.8	16.3	13.8
13	RK	44	4200	0	965	9.6	10.2[a]	8.7[b]
14	RK	15	1200	2	415	11.9	9.9	12.2
15	RK	43	3400	1	310	10.1	12.1	11.8
16	LK	41	2600	2	850	8.7	10.9	10.2
17	RK	21	1800	2	835	10.4	10.9	11.7
18	RK	23	2000	2	675	11.0	10.2	11.0
19	LK	44	3400	2	1035	9.1	10.4	8.4
20	LK	26	1800	3	720	9.3	10.3	9.5
21	RK	42	1600	2	1025	10.5	11.1	11.9
22	BK	54	6600	3	1640	8.6	10.0	8.9
Mean		41	3200	2.3	1022	10.6	11.1	10.6

A Patient no.
B Arthroplasty
H hip
K knee
C Days of treatment
D Total dose of rHuEPO (units/kg)
E Collected blood, units
F Operative blood loss, grams

G–I Hemoglobin levels, g/dL
G Before treatment
H Before operation
[a]after 1 unit of preoperative homologous blood transfusion
I After operation
[b]after 1 additional unit of intraoperative homologous blood transfusion

The hemoglobin response ratio to rHuEPO = The estimated hemoglobin increase (g/dL) / total dose of rHuEPO per kg body weight (units/kg) .

The hemoglobin response ratio to rHuEPO indicated the hemoglobin increase for the total dose of rHuEPO during the treatment. This assessment assumes a blood volume of 6 percent of the total body weight.

Cost analysis

The mean total cost of the rHuEPO treatment in our study was USD 3467 (1083–4803) per patient, and the mean cost of the autologous blood donation was USD 256 (109–327).

Statistics

Student's *t*-test was used for the evaluation of the mean values. The values were considered to be significant if $P < 0.05$. Correlations were assessed by the Spearman rank correlation coefficient.

Table 3. The changes in the clinical and laboratory examinations during rHuEPO treatment. Mean *SEM*

	Before treatment		After treatment		*P*-value
Ritchie index[a]	13.6	*1.4*	13.2	*1.6*	0.4
ESR (mm/hr)	49	*6.6*	41	*5.9*	0.2
CRP (mg/dL)	3.6	*0.6*	2.3	*0.4*	0.001
Total protein (g/dL)	6.8	*0.2*	7.1	*0.1*	0.03
Albumin (g/dL)	3.5	*0.1*	3.8	*0.1*	0.006
Iron (µg/dL)	57	*10*	39	*9.3*	0.2
Ferritin (ng/mL)	122	*66*	82	*55*	0.06

[a] Ritchie articular index was assessed by numerical measurement of joint tenderness according to Ritchie et al. (1968).

Results

Before treatment, the mean hemoglobin concentration for the whole group was 11 (7.4–14) g/dL. The mean hematocrit value was 33 (22–44) percent. The mean baseline erythropoietin level was 29 (12–56) µunits/mL.

Of the 22 patients investigated, 21 responded to the therapy and were able to donate at least 1 unit of autologous blood before operation, without any decrease in hemoglobin concentration. The mean amount of collected autologous blood was 2 (1–3) units. The mean donation period (from the day of the first rHuEPO administration to the day of operation) was 41 (15–62) days (Table 2). The operations in all cases were performed within 6 weeks after the first donation, which is the limit for blood preservation.

In the hip operations, the mean total operative blood loss was 1168 (720–1855) g and in TKA, the total blood loss was 847 (310-1640) g (Table 2). None of the 21 patients who were able to contribute autologous blood preoperatively required any homologous blood transfusions. There were no decreases in the hemoglobin concentrations after donations, and the postoperative anemia was mild (Figure 1).

In Case 13 who had severe anemia, even in spite of receiving high doses of rHuEPO treatment, no erythropoiesis was demonstrated during the treatment. The total dose of rHuEPO given to this patient over 44 days was 144,000 units (4,200 units/kg body weight). No lesion could be found in her gastroduodenal tract. In this case, due to the lack of any autologous blood donation, 1 unit of homologous blood had to be transfused before the operation and 1 unit of blood was needed during the operation. She had a very active inflammation with low initial serum iron and ferritin levels, and the serum iron level did not increase in spite of the oral administration of iron (Table 2).

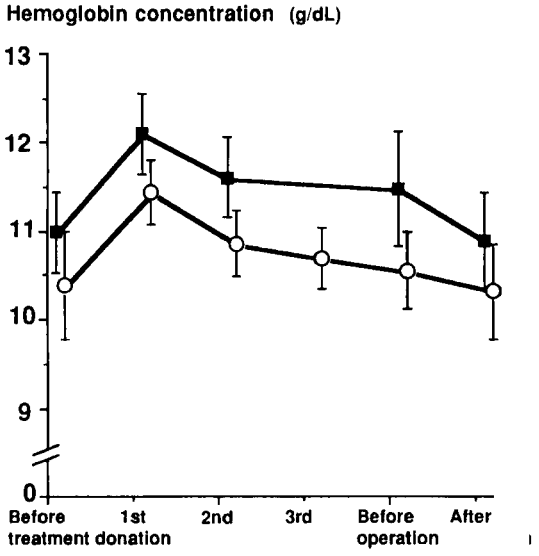

Figure 1. The changes of hemoglobin concentrations in patients from whom either 2 units of autologous blood (filled squares) or 3 units of autologous blood (hollow circles) were collected. Each point represents the means ± SEM. The hemoglobin concentrations were measured on the day before beginning the rHuEPO treatment, the day before each donation (2 or 3 in all), the day before operation and 2 days after operation.

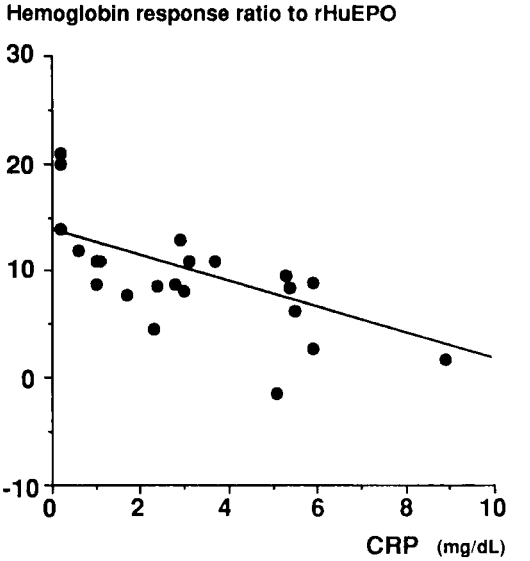

Figure 2. The relationship between the initial CRP levels and the hemoglobin response ratio to rHuEPO in 22 patients. The hemoglobin response ratio to rHuEPO was calculated as described in the text. The hemoglobin response ratio to rHuEPO demonstrated a negative correlation to the CRP levels ($y = 14.0–1.2x$; $r = 0.46$; $P = 0.02$).

We examined the relationship between the various indices of disease activity and the hemoglobin response ratio to rHuEPO in all patients; there was a tendency for the hemoglobin response ratio to correlate negatively with the initial CRP levels (Figure 2).

The effect of rHuEPO treatment on the rheumatological clinical status was also evaluated. There were no differences in the Ritchie articular index, the Steinbrocker functional class, the erythrocyte sedimentation rate, or the serum iron and ferritin levels before and after rHuEPO treatment. However, there was a decrease in the CRP levels and an increase in the total protein and albumin levels after the treatment (Table 3).

Discussion

The anemia in patients with chronic inflammatory arthritis is a well-characterized clinical entity, but its pathogenesis still remains unclear. The major factors in the anemia of RA have been suggested to be marrow insufficiency (Hansen 1983), a shortened red cell survival, an impaired release of iron from the reticuloendothelial system, and a failure of the marrow to respond to the stimulus of anemia (Cartwright 1966). It was recently reported that interleukin-1 suppresses the proliferation of erythrocyte progenitor cells (Schooley et al. 1987, Smith et al. 1992). We have also found that the hemoglobin response ratio to rHuEPO correlates negatively with CRP levels, which indicates that the activity of rheumatologic inflammation is one of the major factors influencing the response to rHuEPO. This is consistent with the finding that, in RA patients with high disease activity, the plasma interleukin-1 level was elevated (Eastgate et al. 1988).

Means et al. (1989) first reported that anemic RA patients can respond to rHuEPO with meaningful changes in both the hematocrit level and in red cell mass, but no meaningful changes in the scores for activity of daily living and pain were seen. Others have also demonstrated excellent hematologic responses to rHuEPO in RA patients, although no meaningful changes in rheumatologic clinical status were seen in their studies (Pincus et al. 1990, Takashina et al. 1990, Gudbjörnsson et al. 1992). These results indicate that rHuEPO is not effective for improving the rheumatologic clinical status. We think that the clinical value of rHuEPO treatment in RA patients is questionable if it is administered only for the treatment of anemia. We believe that rHuEPO treatment for autologous blood donation in patients with RA undergoing elective surgery is the most useful method for administering rHuEPO because it can prevent homologous blood

transfusion-related diseases, such as hepatitis B or C, HIV and graft-versus-host disease, after operations.

Our observations suggest that patients with anemia in chronic disorders due to other inflammatory conditions or malignancy who are undergoing elective surgery might also benefit from rHuEPO.

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