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Quality of life and exercise capacity in anaemic hemodialysis patients treated with erythropoietin

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Placebo-controlled trials have demonstrated that recombinant human erythropoietin increases the hemoglobin level in anaemic hemodialysis patients [1-3]. However, no placebo-controlled studies have evaluated the effect of erythropoietin upon the quality of life of these patients. A number of uncontrolled, before-after studies have shown an increase in exercise capacity in erythropoietin-treated hemodialysis patients. However, these patients have not been randomly selected from a hemodialysis population, and therefore, in general, one suspects that the patients were selected partly because they were judged particularly likely to benefit from erythropoietin.

The Canadian Erythropoietin Study Group has performed a randomized, double-blind, placebo-controlled study in anaemic hemodialysis patients to determine: a) whether erythropoietin improves the quality of life and exercise capacity of anaemic hemodialysis patients, and b) the optimal hemoglobin level for these patients.

Study design

The design of the study has been described in detail previously [4]. Briefly, 118 anaemic hemodialysis patients with a hemoglobin level of less than 90 g/l were randomized into three groups to receive: placebo, erythropoietin at a dose adjusted to maintain the hemoglobin level between 95 to 110 g/l, and erythropoietin adjusted to maintain the hemoglobin level between 115 and 130 g/l. The initial dose of erythropoietin was 100 u/kg/dose, injected intravenously at the end of each dialysis three times weekly. The erythropoietin dose was then adjusted to achieve the target hemoglobin level.

Three quality of life outcome measures were used. The Kidney Disease Questionnaire was developed by asking hemodialysis patients to identify those aspects of their quality of life that had been adversely affected by their disease, following the format suggested by Guyatt et al. [5] It has five dimensions: fatigue, physical symptoms, relationships with others, depression and frustration. The responses were scored on a 7-point Lickert scale, with 1 representing a severe problem, and 7 no problem. The Sickness Impact Profile is a behaviously-based questionnaire that consists of 12 dimensions, which can be aggregated into global, physical and psychosocial domains [6]. A lower score indicates a better quality of life. This questionnaire has been used in a large survey of quality of life in patients with end-stage renal disease in the United States [7]. The time trade-off is a method of measuring a utility, and essentially reflects the number of years of their current health state that patients would be willing to forgo for perfect health [8]. Possible scores range from 0 (equivalent to being indifferent between life and death) and 1 (perfect health).

Exercise capacity was assessed by a modified Naughton treadmill test [9] and a six minute walk test [10].

The study outcome measures were administered in a standard order on non-dialysis days prior to randomization, and two, four and six months after randomization. Analysis of the outcome parameters was performed on patients who had completed all four evaluations using an analysis of variance for repeated measures.

The study was double-blind in that neither the patient, study nurse nor physician knew which therapy the patient had been allocated to. One unblinded physician per centre adjusted the erythropoietin dose, but had no contact with the patients.

After the six months of the randomized trial were complete, the placebo patients were offered erythropoietin.

Results

Patient characteristics

The patient characteristics are shown in table I. All prognostic factors were evenly distributed among the groups except for time on dialysis ($p = 0.07$ among groups). When this imbalance was corrected, the results of the study were not affected.

Hemoglobin response

The mean hemoglobin at six months was 74 ± 12 g/l (±SD) in the placebo group, 102 ± 10 g/l

Table I. Patient characteristics

	Placebo	Low EPO	High EPO
Age (year)	48 ± 16	44 ± 16	43 ± 15
Sex (% male)	63	48	68
Anephric (%)	15	32	26
Time on dialysis (years)	2.5 ± 3.1	4.6 ± 4.7	4.4 ± 5.1
Hemoglobin (g/l) AT	71	69	71
Baseline	—	—	—

in the low erythropoietin group and 117 ± 14 g/l in the high erythropoietin group. The mean dose of erythropoietin at six months was 204 ± 167 u/kg/week for the low erythropoietin group and 248 ± 146 u/kg/week for the high erythropoietin group.

Quality of life and exercise capacity

The effect of erythropoietin on quality of life and exercise capacity is shown in table II. There was a marked statistically and clinically important improvement in the fatigue, physical symptoms and relationships dimensions of the Kidney Disease Questionnaire, as well as the physical domain of the Sickness Impact Profile in erythropoietin-treated patients. Patients were able to walk further on the stress test after erythropoietin. There was no improvement in frustration measured by the Kidney Disease Questionnaire, the time trade-off score or the six minute walk test.

There was no difference in the improvement in quality of life between patients randomized to the low erythropoietin group, when compared with the high erythropoietin group. There was a correlation between the change in hemoglobin and the change in quality of life during the six months of the trial, but this was relatively weak. The strongest correlation was seen between the change in hemoglobin and the change in the fatigue dimension of the Kidney Disease Questionnaire: $r = 0.32$, $p = 0.001$.

Adverse effects

a) *Hypertension*

Diastolic blood pressure was significantly increased in the erythropoietin-treated patients compared with the placebo-treated patients during the six month study period. The most striking increase was seen in the high erythropoietin group, whose mean diastolic blood pressure increased by 7 mmHg. This increase in blood pressure occurred despite an increase in anti-hypertensive medications during the trial in 27 % of erythropoietin-treated compared with 9 % of placebo-treated patients. When patients who received placebo during the randomized trial were given erythropoietin (at an initial dose of 50 u/kg/dose three times weekly), the mean change in diastolic blood pressure was an increase of 7 mmHg.

There was no difference in the incidence of severe hypertension (defined as a diastolic blood pressure greater than 110 mmHg at least once during the trial or

Table II. Quality of life and exercise capacity measures

	Placebo months 0	Placebo months 6	Low EPO months 0	Low EPO months 6	High EPO months 0	High EPO months 6	Statistical significance
Kidney disease questionnaire							
Physical	4.2	4.6	3.6	5.2	3.9	5.3	< .001
Fatigue	4.4	4.5	4.1	5.0	4.2	5.3	< .001
Relationships	4.9	5.0	4.9	5.5	4.9	5.5	.001
Depression	5.0	5.1	4.7	5.1	4.8	5.5	.018
Frustration	4.9	4.9	4.9	4.9	4.5	4.9	NS
Sickness impact profile							
Global	10.3	7.4	12.0	6.7	12.2	4.4	.024
Physical	4.9	4.2	6.4	2.6	6.3	2.4	.005
Psychosocial	9.1	4.8	10.9	6.0	11.8	3.0	NS
Time trade-off	0.42	0.42	0.49	0.51	0.52	0.58	NS
Stress test (minutes walked)	11.4	13.2	11.2	14.8	16.1	19.7	.018
Six minute walk test[c] (meters walked)	421	440	418	451	470	521	NS

For statistical significance the following hypothesis was tested: there is no difference in response profile between placebo and Low and High Epo groups (i.e. placebo versus erythropoietin).
KDQ: Kidney Disease Questionnaire. SIP: Sickness Impact Profile. TTO: Time Trade-off.
For the SIP, the lower the score, the better the quality of life; for the other measures a higher score indicates a better quality of life.

the occurrence of a hypertension-related seizure) between placebo and erythropoietin-treated patients (13 % and 14 % respectively). Erythropoietin patients were more likely to develop severe hypertension if they were previously receiving antihypertensive medications (27 % versus 8 %).

b) *Other adverse effects*

Nineteen patients were withdrawn from the study: eight patients in the placebo group (transplantation 5, non-compliance 1, transfusion-reaction 1 and seizure-death 1), six patients in the low erythropoietin group (transplantation 2, hypertension 1, hypertension/seizure 1, subarachnoid hemorrhage/seizure 1, pregnancy 1), and five patients in the high erythropoietin group (transplantation 3, hypertension 2). There was a positive association between erythropoietin treatment and the incidence of access clotting ($p = 0.005$) and eye redness ($p = 0.04$). At six months there was a mean increase in platelet count of 24,000 in the erythropoietin-treated patients ($p = 0.005$ compared with placebo-treated patients).

Discussion

As in other studies, erythropoietin was extremely effective at increasing the hemoglobin level in anaemic hemodialysis patients. In general, erythropoietin-treated patients had a marked statistically and clinical important improvement in fatigue and physical symptoms. Erythropoietin-treated patients were able to walk further on an exercise stress test, although there was no difference among groups on the six minute walk test or time trade-off scores.

The relatively weak correlation between the change in hemoglobin throughout the trial and the change in quality of life probably indicates that many factors other than anaemia (e.g. azotemia, bone disease, and the psychological burdens of hemodialysis) adversely affect the well-being of hemodialysis patients, and these factors were not improved by erythropoietin.

During the six months of the study, erythropoietin-treated patients were not more likely to return to work than placebo-treated patients. However, it is possible that more prolonged follow-up will demonstrate a beneficial effect of erythropoietin upon the ability of hemodialysis patients to return to work, although many factors in addition to health affect employment (e.g. education, type of work)[11].

Severe hypertension was equally common in placebo and erythropoietin-treated patients. However, patients who received erythropoietin had a mean increase in diastolic blood pressure of 7 mmHg, during the first six months of therapy, despite an increase in antihypertensive medications. Patients with end-stage renal disease are at high risk for cardiovascular complications, and therefore careful, prolonged follow-up of a large number of erythropoietin-treated patients is needed to ascertain the effect of erythropoietin induced hypertension on long-term morbidity.

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References

1. Eschbach JW, Egrie JC, Downing MR, Browne JK and Adamson JW: Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. *N Engl J Med* 316:73-78, 1987.
2. Winearls CG, Pippard MJ, Downing MR, Oliver DO, Reid C and Cotes PM: Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *Lancet* 1175-1178, 1986.
3. Lim VS, DeGowin RL, Zavala D, Kirchner PT, Abels R, Perry P and Fangman J: Recombinant human erythropoietin treatment in pre-dialysis patients. *Ann Int Med* 110:108-114, 1989.
4. The Canadian Erythropoietin Study Group: The effect of recombinant human erythropoietin on the quality of life and exercise capacity of patients on hemodialysis (in press).
5. Guyatt GH, Bombardier C and Tugwell P: Measuring disease-specific quality of life in clinical trials. *Can Med Assoc J* 134(8):889-895, 1986.
6. Bergner M, Bobbitt RA, Carter WB and Gilson BS: The Sickness Impact Profile: Development and final revision of a health status measure. *Med Care* XIX:787-805, 1981.
7. Hart LG and Evans RW: The functional status of ESRD patients as measured by the Sickness Impact Profile. *J Chron Dis* 40:117S-130S, 1987.
8. Churchill DN, Torrance GW, Taylor DW et al.: Measurement of quality of life in end-stage renal disease: the time trade-off approach. *Clin Invest Med* 10:14-20, 1987.
9. Naughton J, Sevelius G and Balke B: Physiological responses of normal and pathological subjects to a modified work capacity test. *J Sports Med Phys Fitness* 3:201-207, 1963.
10. Guyatt GH, Sullivan MJ, Thompson PJ et al.: The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 132:919-923, 1985.
11. Smith GR and O'Rourke DR: Return to work after a myocardial infarction. *JAMA* 259:1673-1677, 1988.