Transplant Int (1992) 5 [Suppl 1]: S 104–S 106

TRANSPLANT
International

Renal transplantation in r-HuEPO-treated patients

A. O. Seeberger[1], A. Tibell[2], and G. Tydén[2]

[1] Department of Nephrology and [2] Department of Transplantation Surgery, Karolinska Institute, Stockholm, Sweden

Abstract. After sporadic reports of renal graft artery thromboses, prophylaxis against thrombosis (PAT) was given to all of our r-HuEPO-treated patients ($n = 35$) during a period of 2 years. No thromboembolic events (TEE) occurred in the r-HuEPO-treated group receiving PAT. However, the PAT-protocol (500 ml dextran on days 0, 1, 3 and 5, followed by low doses of aspirin, 160–250 mg daily) resulted in a 54.3% incidence of bleeding complications, of which 22.9% were major (i.e., necessitating multiple transfusions or invasive procedures). A group of renal graft recipients ($n = 83$), who were not treated with r-HuEPO and were not given PAT, showed a 10.8% incidence of bleeding complications of which 2.4% major. Two cases of TEE were noted in the untreated group. The difference in bleeding complications between the two groups was statistically significant ($0.025 > P > 0.01$). The difference in TEE between the groups was not significant. We found no difference between the groups with regard to early and late graft function and the incidence of acute rejections. In summary, r-HuEPO treatment did not influence the prognosis in renal graft recipients. The use of PAT in the r-HuEPO-treated group resulted in a high incidence of bleeding complications. In consequence, we have abandoned the routine use of PAT in this patient group.

Key words: Renal transplantation – Recombinant human erythropoietin – Prophylaxis against thrombosis

The clinical use of recombinant human erythropoietin (r-HuEPO) has dramatically improved the treatment of uraemic patients. r-HuEPO not only corrects their renal anaemia but also improves their physical condition as reflected by a better appetite and exercise capacity, as well as a reversal of various hormonal and metabolic aberrations, which result in an improvement in their quality of life [1, 5]. However, adverse effects have also been reported, such as hypertension, seizures, diminished dialysis efficiency and clotting of arteriovenous fistulas and grafts [4]. There has also been concern about an increased risk of thromboembolic events (TEE) when performing renal transplantations. After sporadic reports of renal graft artery thromboses, prophylaxis against thrombosis (PAT) was given to all of our r-HuEPO-treated renal graft recipients. The efficiency and side-effects of PAT in this patient group were analysed in the present study.

r-HuEPO treatment has also been shown to influence the immunological response in uraemic patients [3]. We therefore studied the incidence of acute rejections and 1-year graft survival. In addition, early graft function was evaluated, because animal studies have shown that an increase in haematocrit aggravates reperfusion damage during kidney transplantation, thereby worsening early graft function [11].

Materials and methods

A total of 118 adult patients who received a renal transplant during a period of 2 years (June 1988 to June 1990) were studied retrospectively. Of these patients, 35 (group A) had been treated with r-HuEPO, and they were therefore given prophylaxis against thrombosis (PAT) (500 ml dextran on days 0, 1, 3 and 5, followed by low-dose aspirin 160–250 mg daily). The other 83 patients (group B) were not treated with r-HuEPO, and they were therefore not given PAT. The mean haemoglobin value in the r-HuEPO-treated group was 100 ± 15 g/l and in the untreated group 90 ± 20 g/l. The difference in haemoglobin levels between the two groups was statistically significant ($P = 0.005$). Other patient characteristics are shown in Table 1.

Table 1. Patient characteristics

	r-HuEPO + ATP ($n = 35$)	No r-HuEPO + no ATP ($n = 83$)
Mean age (years)	45.7	47.9
Diabetes	11.4%	14.5%
HD before transplant	88.6%	71.1%
PD before transplant	11.4%	15.7%
LD grafts	14.3%	22.9%

Offprint requests to: Dr. G. Tydén, Department of Transplantation Surgery, Karolinska Institute, Stockholm, Sweden.

Table 2. Bleeding complications

	GI bleeding	Haematuria	Haematoma
r-HuEPO + PAT ($n = 35$)	5 (4 major)	8 (4 major)	6 (1 major)
No r-HuEPO, no PAT ($n = 83$)	2 (2 major)	3	4

Table 3. Serum creatinine levels (μmol/l)

	Day 7	Day 30	6 months	12 months
r-HuEPO + PAT ($n = 35$)	277 ± 120	208 ± 129	195 ± 122	164 ± 67
No r-HuEPO, no PAT ($n = 83$)	319 ± 297	184 ± 114	189 ± 144	154 ± 59
P value	0.2473	0.0247	0.0814	0.1884

Table 4. Graft loss during the first year after renal transplantation

	r-HuEPO + PAT ($n = 35$)	No r-HuEPO, no PAT ($n = 83$)
Acute vascular rejection	3	8
Chronic rejection	2	2
Non-functioning graft	1	1
Graft artery thrombosis	0	1
Carcinoma in renal graft	0	2
Immunosuppressive treatment removed	1	0

Statistical analyses were performed with the paired Student's *t*-test and the chi-squared test. Values are given as means ± SD.

Results

No TEE occurred in the r-HuEPO-treated patients receiving PAT (group A). In the untreated group (group B), two cases of TEE were noted (one renal graft artery thrombosis, one deep vein thrombosis). The difference in TEE between the groups was not significant. However, PAT in group A resulted in a 54.3 % incidence of bleeding complications, of which 22.9 % were major, i.e. necessitating multiple transfusions or invasive procedures (see Table 2). No grafts were lost because of these complications. Group B, which was not given PAT, showed a 10.8 % incidence of bleeding complications, of which 2.4 % were major. The difference in bleeding complications was statistically significant both for the total number of complications ($0.025 > P > 0.01$) and for the number of major cases ($0.025 > P > 0.01$). All bleeding complications were observed during the first month after transplantation.

Early graft non-function was defined as an inability to reduce the serum creatinine level on day 1 after transplantation. Early graft non-function was shown by 18 patients in group A (51.4 %) and 37 patients in group B (46.6 %). There was no statistically significant difference between the groups. Eight patients in group A (22.9 %) and 14 patients in group B (16.9 %) required dialysis during the first week after transplantation. There was no statistically significant difference between the creatinine levels in the two groups on day 7 and day 30 and after 6 and 12 months (Table 3).

Ten patients in group A (28.6 %) and 25 patients in group B (30.1 %) did not have a single episode of acute rejection, 14 patients in group A (40.0 %) and 33 patients in group B (39.8 %) had one episode, and 11 patients in group A (31.4 %) and 25 patients in group B (30.1 %) had more than one episode. Three patients in group A (8.6 %) and eight patients in group B (9.6 %) had irreversible rejections. Another four patients in group A (20.0 %) and six patients in group B (16.9 %) lost their grafts during the first year (Table 4). Two patients in group A (5.7 %) and three patients in group B (3.6 %) died during the first year.

Discussion

There has been concern about an increased incidence of TEE in r-HuEPO-treated patients. r-HuEPO increases the haematocrit which results in an increased blood viscosity [8]. Plasma viscosity is not changed by r-HuEPO treatment [10]. Moreover, the platelet count increases significantly during the initial phase of r-HuEPO treatment, but thrombocytosis rarely develops [7]. Platelet adhesion has been shown to increase, while prothrombin, partial thromboplastin time and fibrinogen levels remain unchanged [6]. Bleeding time is shortened by r-HuEPO treatment [6]. Thus r-HuEPO influences several factors which may lead to an increased incidence of TEE.

However, it has yet not been shown that r-HuEPO increases the incidence of coronary, cerebral or peripheral thromboses nor has any study convincingly shown that r-HuEPO treatment is accompanied by an increased risk of vascular access clotting. The reported cases of fistula or shunt thromboses all occurred in patients with 'fistulae-on-risk', such as earlier clotting problems or a technically complicated vascular situation [2, 9].

In 1988 sporadic reports of renal graft artery thrombosis in r-HuEPO-treated patients appeared [12]. In consequence of this, we introduced the use of antithrombotic prophylaxis in all of our r-HuEPO-treated renal graft recipients. Since then, no TEE has occurred in the EPO-treated patients compared with two cases in a group that received neither r-HuEPO nor PAT, but this difference was not statistically significant. However, the protocol resulted in a high incidence of both postoperative and biopsy-related bleeding complications, of which many were major. All the bleeding complications were observed during the first month after transplantation. No graft was lost because of such complications.

Animal studies have shown that a lower haematocrit in rats receiving renal grafts results in better early graft function, independently of preservation time and type of preservation solution [11]. We found a significant difference in haemoglobin levels between our two groups, but no difference with regard to early graft function.

r-HuEPO treatment has been shown to reduce the number of HLA antibodies in some patients [3]. A significant decrease in PRA response and a decrease in T-cell subsets during r-HuEPO treatment has also been reported. We detected no significant difference between our two groups with regard to the incidence of acute rejection and 1-year graft survival.

In summary, no differences between the groups were noted in early and late graft function nor in the incidence of acute rejections. No thromboembolic events occurred in r-HuEPO-treated patients. However, the use of PAT in the r-HuEPO-treated group resulted in a high incidence of bleeding complications. In consequence, we have abandoned the routine use of PAT in this patient group. If PAT is required, the protocol should be less stringent.

References

1. Canadian Erythropoietin Study Group (1990) Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving hemodialysis. Br Med J 300: 573–578
2. Eschbach JW, Downing MR, Egrie JC, Browne JK, Adamson JW (1989) USA multicenter clinical trial with recombinant human erythropoietin. In: Baldamus CA, Scigalla P, Wieczorek L, Koch KM (eds) Erythropoietin: from molecular structure to clinical application. (Contributions to Nephrology, vol 76) Karger, Basel, pp 160–165
3. Grimm GC, Sinai-Trieman L, Sekiya NM, Robertson LS, Robinson BJ, Fine RN, Ettenger RB (1990) Effect of recombinant human erythropoietin on HLA sensitization and cell-mediated immunity. Kidney Int 38: 12
4. Gruetzmacher P, Bergmann M, Weinreich T, Nattermann U, Reimers E, Pollok M (1988) Beneficial and adverse effects of correction of anaemia by recombinant human erythropoietin in patients on maintenance haemodialysis. Contrib Nephrol 66: 104
5. Kokot F, Wiecek A, Greszczak W, Klepacka J, Klin M, Lao M (1989) Influence of erythropoietin treatment on endocrine abnormalities in haemodialyzed patients. In: Baldamus CA, Scigalla P, Wieczorek L, Koch KM (eds) Erythropoietin: from molecular structure to clinical application. (Contributions to Nephrology, vol 76) Karger, Basel, pp 257–272
6. Moia M, Mannuci PM, Vizzotto L, Casati S, Cattaneo M, Ponticelli C (1987) Improvement in the haemostatic defect of uraemia after treatment with recombinant human erythropoietin. Lancet I: 1227–1229
7. Samtleben W, Baldamus CA, Bommer J, Gruetzmacher P, Nonnast-Daniel B, Scigalla P, Gurland HJ (1989) Indications and contraindications for recombinant human erythropoietin treatment. In: Baldamus CA, Scigalla P, Wieczorek L, Koch KM (eds) Erythropoietin: from molecular structure to clinical application. (Contributions to Nephrology, vol 76) Karger, Basel, pp 193–200
8. Schäfer RM, Leschke M, Strauer BE, Heidland A (1988) Blood rheology and hypertension in hemodialysis patients treated with erythropoietin. Am J Nephrol 8: 449–453
9. Scigalla P, Bonzel KE, Bulla M, Burghard R, Dippel J, Geisert J, Leumann E, v. Lilien T, Mueller-Wiefel DE, Offner G, Pistor K, Zoellner K (1989) Therapy of renal anemia with recombinant human erythropoietin in children with end-stage renal disease. In: Baldamus CA, Scigalla P, Wieczorek L, Koch KM (eds) Erythropoietin: from molecular structure to clinical application. (Contributions to Nephrology, vol 76) Karger, Basel, pp 227–241
10. Vaziri ND, Ritchie C, Brown P, Kaupke J, Atkins K, Barker S, Hyatt J (1989) Effect of erythropoietin administration on blood and plasma viscosity in hemodialysis patients. Trans Am Soc Artif Intern Organs 35: 505–508
11. Wahlberg J, Jacobsson J, Odlind B, Tufveson G, Wikström B (1988) Haemodilution in renal transplantation in patients on erythropoietin. Lancet II: 1418
12. Zaoui P, Bayle F, Maurizi J, Foret M, Dalsoglio S, Vialtel P (1988) Early thrombosis in kidney grafted into patient treated with erythropoietin. Lancet II: 956