Increase in mean platelet volume in patients with chronic renal failure treated with erythropoietin

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Abstract
Aims—To assess whether r-HuEPO (recombinant human erythropoietin) has any effect on thrombopoiesis in patients with chronic renal failure.

Methods—This was a retrospective study of 78 patients with chronic renal failure undergoing either haemodialysis (n = 57) or intraperitoneal dialysis (n = 21). All patients had a full blood count (in EDTA) measured before starting r-HuEPO and at monthly intervals thereafter up to six months. Variables studied were haematocrit, platelet count, mean platelet volume (MPV) and platelet distribution width (PDW). Other groups of control patients were also studied—patients with chronic renal failure receiving dialysis but not r-HuEPO (n = 40) and a group of patients with normal renal function who were receiving aspirin (n = 30).

Results—There was a significant increase in mean haematocrit (p < 0.01) and in mean platelet volume (p < 0.001) over the six month period, but no change in either total platelet count or platelet distribution width in the patients with chronic renal failure receiving r-HuEPO. In contrast, both the control groups showed no significant change in MPV.

Conclusions—The results suggest that r-HuEPO affects thrombopoiesis and may be part of a group of humoral factors contributing to megakaryocyte development and maturation. Larger platelets are more reactive and may contribute to the increased risk of thrombosis associated with r-HuEPO.

(J Clin Pathol 1994;47:159–161)

Chronic renal failure is associated with bleeding problems, indicated by decreased platelet aggregation and prolonged bleeding times.\(^1\)\(^2\) Patients receiving r-HuEPO (recombinant human erythropoietin) treatment show improved haemostasis and increased platelet aggregation,\(^3\)\(^4\) and one of the well known side effects of r-HuEPO is an increased risk of thrombosis.\(^7\) Recent evidence has shown that larger platelets are more reactive per unit volume than smaller platelets and are more likely to aggregate, leading to thrombosis.\(^8\)\(^9\)\(^10\) Large platelets seem to be an independent risk factor for myocardial infarction, and platelet size is one predictor of recurrent myocardial infarction and death.\(^10\)

It is now known that there are receptors for EPO on the megakaryocytes of rats and mice\(^11\)\(^12\) and that platelet size is determined at or before the megakaryocyte budding stage.\(^13\) It has also been shown that r-HuEPO acts as a humoral growth factor and promotes differentiation of murine megakaryocytes.\(^14\)

Methods
This was a retrospective study of 78 patients (40 men and 38 women), whose ages ranged from 17 to 84 years (mean age 56 years) with chronic renal failure receiving r-HuEPO (Epred) under the care of the regional renal unit in Belfast City Hospital. Fifty seven of the patients were undergoing haemodialysis (on one to three times a week) and the other 21 were receiving intraperitoneal dialysis (IPD). All patients had normochromic, normocytic anaemia associated with renal failure; other causes of anaemia had been excluded by regular measurements of serum ferritin, vitamin B\(_12\) and folate. Forty of the 78 patients were receiving regular supplemental iron-dextran injections.

The dose of r-HuEPO began at 50 IU/kg twice weekly (by subcutaneous injection), increasing to 75 IU/kg twice weekly after two to three months if there was an insufficient rise in haematocrit and haemoglobin. It is the policy of the renal unit to give aspirin to all patients starting r-HuEPO. Twelve out of the 78 patients did not receive aspirin during the six month period of study as they had been given r-HuEPO before the establishment of this policy.

All the patients had a full blood count (in EDTA) measured on a Coulter STKS (Coulter Electronics, Northwell Drive, Luton, Beds) at monthly intervals from baseline (before starting r-HuEPO) up to six months. As a result of organisational procedure both within the renal wards and the haematology laboratory, most of the samples would have been analysed within 4 hours of venepuncture, but we cannot exclude a few samples having been analysed at a later time. The variables studied were haematocrit, platelet count, mean platelet volume (MPV) and platelet distribution width (PDW).

Changes in these variables were compared with baseline values and statistically analysed using Student’s paired t test. A measure of the difference between the maximum value of a variable achieved over the six month period and baseline was calculated and used in the
analyses of the various subgroups (men/women; age groups; haemodialysis/intraperitoneal dialysis, etc) using the unpaired $t$ test.

A group of 40 patients with chronic renal failure not receiving r-HuEPO but undergoing dialysis was also followed up from baseline (before starting dialysis) up to six months (22 men and 18 women, age range 24–78 years, mean 51·3 years; 29 receiving haemodialysis, 11 intraperitoneal dialysis). Unfortunately we were unable to obtain a full set of perfectly age and sex matched controls due to insufficient numbers.

A group of 30 patients who had had a myocardial infarction (post myocardial infarct) but normal renal function (16 men and 14 women) who were all given aspirin at diagnosis were also studied at baseline, three months, and six months (blood was analysed within 4 hours of venepuncture).

The control patients (those receiving dialysis but not r-HuEPO and the post myocardial infarct group receiving aspirin) were analysed using the paired $t$ test.

discussion

We have shown a significant increase in mean platelet volume (MPV) ($p < 0.001$) in a group of patients with chronic renal failure treated with r-HuEPO. The dialysis process itself and medications such as aspirin and iron-dextran injections do not seem to affect the MPV. The increase in MPV does not
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We thank the renal physicians and nursing staff of the Belfast City Hospital for allowing us to study these patients. Thanks also to Mrs Barbara Scott, Mr Derek Sterling, and Mr Cieran Ems for their assistance with the manuscript.

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