Is the use of recombinant human erythropoietin in anaemia of prematurity cost-effective?

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In a double-blind placebo-controlled study we showed a 3-fold decrease in blood transfusions (BTFs) given to preterm infants with anaemia of prematurity who received recombinant erythropoietin. However, only 50% of placebo recipients required a BTF. Data from the placebo group indicated that either mean daily weight gain ≤ 7.5 g/day before study entry or haematocrit ≤ 50% at birth was associated with BTFs ($P < 0.001$). We calculated that giving erythropoietin to patients in the treatment group with either of these variables prevented 24 of 28 BTFs and that it would cost R184 to prevent 1 BTF. The cost of each BTF was R187 (blood filtered to remove white cells and reduce cytomegalovirus transmission). Therefore, the costs of the two treatments were similar, but as the risk of transmitting infection is lower with erythropoietin, we recommend its use in selected preterm infants.

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Recombinant human erythropoietin (rHuEpo) decreases blood transfusion (BTF) requirements in preterm infants with anaemia of prematurity. The European multicentre study showed a 1.4-fold reduction[1] while a double-blind placebo-controlled study carried out at Groote Schuur Hospital demonstrated a 3-fold decrease in transfusions in the treatment group.[2]

In the latter study, however, only 19 of 39 (49%) infants in the placebo group received one or more BTFs during the study period. Other workers have reported similar findings.[3] Therefore, the treatment of all preterm infants < 33 weeks' gestation with rHuEpo results in unnecessary use of the drug and increases the cost significantly.

We sought retrospectively to identify a group of preterm infants at higher risk for BTF and to compare the costs of rHuEpo and BTF in such infants. We asked the following questions: (*i*) were there risk factors for BTF among the preterm infants in the placebo group (identifiable prior to study entry)?; (*ii*) would the use of rHuEpo reduce BTFs in patients with these risk factors?

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Methods

Patients

The study population has been described previously[2] and consisted of 80 stable growing preterm infants (birth weight ≤ 1 390 g, gestation < 33 weeks, central haematocrit ≤ 35%). Randomisation was carried out at study entry; infants received subcutaneous rHuEpo (Eprex 600 U/kg/wk) or an equivalent volume of placebo for up to 6 weeks (mean duration of study 28 days). Infants were given BTFs according to a strict protocol as outlined below:

1. Haematocrit < 30% and (*i*) weight gain of < 10 g/day averaged over a 1-week period (infant tolerating full oral feeds and receiving adequate calories); (*ii*) three or more episodes of apnoea (respirations absent for 20 seconds) or bradycardia (heart rate < 100/min) in a 24-hour period not due to other causes and not responsive to methylxanthine treatment; (*iii*) tachycardia (> 170/min) or tachypnoea (> 70/min) sustained over a 24-hour period or associated with acute cardiac compensation; (*iv*) a requirement for surgery;
2. Development of a clinically significant patent ductus arteriosus;
3. Pulmonary disease and fractional inspired oxygen concentrations increasing by > 10% per week;
4. Systemic infection associated with a sudden decrease in haematocrit;
5. Haematocrit of 22% or less and an absolute reticulocyte count of < 100 000 x 10^9.

Statistics

Data were available for 37 placebo infants (1 died soon after entry and results were missing for 2 infants). Patients were divided into those who received one or more BTFs and those who did not. Variables possibly affecting the need for BTF were analysed by means of logistic regression and discriminant analysis. (The LR and 7M programmes of the BMDP package were used.)

Cost of treatment

The number of BTFs given to infants in the placebo group with risk factors was noted. Similarly the number of BTFs received by patients in the rHuEpo group with the same risk factors was determined, so that the number of BTFs prevented as a result of rHuEpo therapy could be calculated.

The cost of paediatric BTF included the price of an in-line filter to reduce transmission of cytomegalovirus (CMV), blood-giving set, venous cannula and syringe. The cost of rHuEpo therapy was based on a mean study time of 4 weeks and it was assumed that the 1 000 U/ml Eprex vial was used to treat 3 patients simultaneously. The costs of extra oral iron, vitamin E, syringes and needles were also included. Costs of laboratory tests (e.g. full blood count) were assumed to be the same in the two groups.

Results

Results for the variables in the placebo group are shown in Table I. The *P*-values shown were obtained from bivariate logistic regression carried out with the BMDP statistical programme.

Using logistic regression, a number of models were tested for the ability to predict the need for BTF. The final model we chose made use of the mean daily weight gain and haematocrit. A weight gain of ≤ 7.5 g/day from birth to study entry and a haematocrit of ≤ 50% within 48 hours of birth were used as cut-off values. The cut-off values (suggested by discriminant analysis) provided a better prediction than models that used the observed continuous variables, and were easier to apply in practice. It was found that preterm infants with either of these risk factors were more likely to require BTF (odds ratio 43; $P < 0.001$). The sensitivity of these parameters in predicting the need for transfusion was 85%, with a specificity of 88%.

Calculation of costs

Nineteen placebo recipients with one of these two risk factors were identified. They received a total of 21 BTFs (average 1.1/patient, 95% confidence interval 0.64 - 1.72). There were 25 patients in the rHuEpo group with the same risk factors; the total number of BTFs predicted was therefore approximately 28 (25 x 1.1). The actual number given was 4 (95% CI 2.6 - 6.0), i.e. 24 transfusions were prevented (Table II). If the strategy of giving rHuEpo to patients with identifiable risk factors is used, it would cost R184 to prevent one BTF. The cost of transfusion is R187 (blood filtered to reduce CMV).

Table I. Factors affecting the need for BTF in preterm infants (mean ± SD)

	BTF (N = 20)	No BTF (N = 17)	Odds ratio	*P*-value
Haematocrit at birth (%)	51.6 ± 8.3	58.5 ± 7.0	1.12/1% decrease	0.01
Gestational age (wks)	30.0 ± 2.0	30.2 ± 1.3	1.06/wk decrease	0.75
Birth weight (g)	1 050 ± 159	1 040 ± 126	1.05/100g	0.83
Days to regain birth weight	16.9 ± 6.8	11.8 ± 5.6	1.16/d	0.018
Days on oxygen	9.3 ± 11.8	4.4 ± 7.5	1.07/d	0.14
Days to full oral feeds	11.1 ± 3.3	8.3 ± 2.2	1.46/d	0.007
Blood taken pre-study (ml)	4.0 ± 4.0	3.1 ± 1.8	1.10/ml	0.382
Weight gain (g)*	4.9 ± 5.1	9.2 ± 5.6	1.24/g decrease	0.003

*Mean daily gain from birth to study entry.

Table II. Numbers of BTFs given to infants receiving placebo or erythropoietin (high risk — weight gain ⩽ 7,5g/day before study entry or haematocrit ⩽ 50% within 48 hours of birth)

	High risk for BTF	Low risk for BTF
Placebo group		
Total transfusions	21 (17)	3 (3)
Number not transfused	– (2)	– (15)
Erythropoietin group		
Total transfusions	4 (3)	3 (3)
Number not transfused	– (22)	– (12)

Figures in brackets indicate the number of patients in each category.

Discussion

Review of our study data indicates that infants likely to need intervention for anaemia of prematurity can be identified. Early weight gain (i.e. from birth to study entry at a mean age of 28 days) probably reflects illness severity as well as adequacy of protein and caloric intake, factors which have been shown to affect erythropoiesis in preterm infants.[4] The time to establish full oral feeds may also be increased in the sicker infants. A close correlation exists between phlebotomy losses and subsequent BTF.[5] In the present study, total phlebotomy losses from birth to completion of the trial were associated with BTF ($P = 0.04$; results not shown). However, the amounts of blood taken prior to study entry were not. Our relatively conservative approach to blood sampling may have been responsible for the observation that birth weight was not related to the need for BTF; other workers have found higher phlebotomy losses and hence greater BTF requirements in smaller babies.[1,5]

Our results also show that rHuEpo is effective in infants at higher risk for BTF. Use of rHuEpo does not appear to be associated with any significant side-effects. Likely benefits include a lower risk of transmitting infection (HIV, hepatitis, CMV). Furthermore, endogenous erythropoietin production is not suppressed (as occurs after BTF); this may be important in reducing the need for multiple BTFs.

As the costs of the two treatments are similar, the lower risk of transmitting infection favours the use of rHuEpo in preterm infants likely to require BTF.

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Is registrarship a different experience for women?

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Objective. To determine differences between male and female registrars in their subjective perceptions and experience of a paediatrics registrar training programme.

Design. Cross-sectional survey.

Setting. University-affiliated teaching hospitals.

Participants. Thirty-nine paediatrics registrars.

Results. Of the 39 respondents, 18 (46%) were women. Men were older than women (30.4 v. 29.1 years, $P = 0.049$). There were no gender differences in the number of hours worked per week (65.7 v. 67.8 hours, $P = 0.384$) or participation in the training programme. Success rates in postgraduate paediatrics examinations were also similar for the two groups (85% v. 76%, $P = 0.486$). Male registrars were more likely to have 'moonlighted' (43% v. 6%, $P = 0.011$). Fifty-nine per cent of female registrars believed that they had been disadvantaged in their careers because of their gender, 28% felt that more was expected of a woman registrar and 22% of the female trainees claimed to have been subjected to sexual harassment. The majority (82%) of women registrars contemplated taking time off from practising clinical paediatrics in the future (post-registrarship), mainly for child-bearing purposes. Female respondents criticised both the academic department and the hospital authorities for discriminatory practices, such as the awarding of home loans to men and women who were breadwinners only. The findings suggest that women registrars do feel disadvantaged and discriminated against, and highlight the need for flexible, creative programmes that recognise the needs and aspirations of female registrars and, indeed, all women in academic medicine.

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For young women in particular, the demands of registrarship are in conflict with many other demands of life, e.g. time needed to develop a relationship with a partner, the age limits of fertility, time needed to have a baby and for child-rearing. While these conflicts are not new for working women, the increasing number of female registrars, especially in paediatrics, increases their prominence.

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