Financial Impact of the Introduction of Erythropoietin in the Treatment of Anemia of Premature Infants in Israel

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Abstract

Background and Objective: Very low birthweight infants (<1,500 g birthweight) often develop significant anemia that requires multiple blood transfusions, which carry a significant risk. Erythropoietin therapy is known to reduce the need for blood transfusions in preterm VLBW[1] infants. Analysis of cost had been reported in prospective studies with conflicting results. No studies comparing the cost-effectiveness of EPO[2] have been reported during routine use in preterm VLBW infants.

Methods: We compared the cost of treating anemia of prematurity in two consecutive 12-month periods: before and after the introduction of EPO therapy in our unit. The cost of blood bank charges as well as disposable items and the cost of EPO were compared.

Results: A significantly smaller number of infants required blood transfusions in the EPO group (2 of 25 vs. 9/21 before EPO was introduced). The cost of therapy for anemia of prematurity was significantly smaller in the EPO group (128±168 US$ per infant vs. 151±189 US$ per infant before the introduction of EPO).

Conclusion: We conclude that EPO is an efficient and cost-effective alternative to blood transfusions in VLBW infants.

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Erythropoietin is the major hormonal regulator of erythropoiesis. Failure to mount an erythropoietic response appropriate to the level of anemia greatly contributes to the need for multiple blood transfusions, with all their risks, in preterm infants [1]. In spite of efforts to reduce blood sampling in VLBW infants (<1,500 g birthweight), most, especially the smallest, develop anemia. The availability of recombinant DNA-produced EPO has raised the hopes that EPO may significantly reduce the need for blood transfusion in preterm infants. While its efficacy in raising reticulocyte counts and hematocrit has been demonstrated in several randomized controlled trials [2–6], and in a meta-analysis [7], EPO has not become a standard, routinely used drug in anemic preterm infants, and its analysis of cost is still debated [8–13]. In order to test the hypothesis that EPO would lower the need for blood transfusion and is cost-effective, we studied the financial impact and efficacy of treating VLBW infants with EPO by retrospectively comparing two successive periods, one that preceded and one that followed the introduction of EPO in our neonatal intensive care unit.

Patients and Methods

Pre-EPO period

All VLBW infants (<1,500 g) born at the Tel Aviv Sourasky Medical Center were included for analysis. During this period (September 1996 to August 1997), our goal was to maintain blood venous or capillary hematocrit within specific limits (see later), with the help of blood transfusions. Hematocrit was routinely (at least once a week, and more often if clinically indicated) determined by capillary centrifugation (Biofuge, Heraus Instruments, Germany) spun for 5 minutes at 10,000 rpm. Infants were given supplemental iron (4 mg/kg/day) once they reached full enteral feeding. We strictly followed a transfusion protocol as follows:

a) In acutely sick ventilated patients hematocrit was kept above 40%.
b) In ventilated preterm infants with fraction of inspired oxygen >35% or mean airway pressure >6 cmH_2O, hematocrit was kept above 35%.
c) In symptomatic infants, chronically ventilated infants with mean airway pressure ≤6 cmH_2O, or apnea of prematurity >8 in 12 hours, or persistent tachycardia >180/min, or low weight gain (<10 g/day for 4 consecutive days), hematocrit was kept above 30%.
d) In asymptomatic infants with no oxygen requirement, hematocrit was kept above 20%.

EPO period

After the introduction of EPO (September 1997 to August 1998), transfusion guidelines and phlebotomy routines remained unchanged. Inclusion criteria for treatment with EPO were all preterm infants <1,500 g at birth who had reached at least two-thirds of full enteral feeding (at least 100 ml/kg/day) of breast milk or preterm formula with a hematocrit ≤40%. We chose only infants who tolerated feeds, since it enabled us to provide them with supplemental enteral iron with a total elemental iron intake of 4 mg/kg/day.

[1] VLBW = very low birthweight
[2] EPO = erythropoietin

Table 1. Cost in United States dollars of blood bank charges, transfusion supplies and erythropoietin

Item	Cost in U.S. dollars
CMV-negative blood	159.0
Crossmatch with maternal blood	32.5
Crossmatch with neonatal blood	30.0
Maternal blood type performed twice	14.0
Neonatal blood type performed twice	12.5
Direct Coombs test	20.0
Antibody screening (mother)	22.0
Transfusion tubing	1.0
Erythropoietin, cost of one course	71.0

Each unit of blood was divided into 4 aliquots. After the first transfusion, the rest of the aliquots were saved for future transfusions. Each erythropoietin ampule was used to treat 3 patients on any given day of treatment.

Excluded from both periods were infants who were transferred to another institution prior to discharge home, or infants who were not born in our institution.

EPO protocol

An extensive literature review revealed a higher efficacy of EPO when given for a period of 20 days, at more than 600–700 IU/kg weight/week [14,15]. We therefore elected to administer EPO (Eprex, Cilag AG, Schaffhausen, Switzerland) in doses of 200 IU/kg on alternate days for a total of 10 days. Due to our strict feeding protocol, EPO was started in most infants during the second week of life.

Statistical methods and analysis

The efficacy of EPO was determined in terms of reduction in the number of blood transfusions, which were counted for every infant from birth to discharge. Analyses of cost included the combined cost of blood and supplies used for blood transfusion, as well as blood bank charges [Table 1]. These analyses were conducted for both periods. In addition, the cost of EPO was added to the cost of blood transfusions during the second period. In order to decrease EPO costs, all infants received EPO on the same days of the week in order to make full use of EPO ampules, which expire 24 h from opening. On average, 1 ampule of EPO at the cost of $21.3 was used for three infants. Thus the cost of a full 10-dose course averaged at $71 ($21.3/3 x 10). A comparison of the number of transfusions per child and the cost analysis were done using the Wilcoxon test, and the comparison of the percentage of infants requiring transfusion in each group by the Chi-square test. Data are expressed as mean ± SD; a P value of <0.05 was considered significant.

Results

During the study period prior to the introduction of EPO, we attended to 25 VLBW infants, of whom 4 died prior to discharge and were excluded. No infant was excluded from the study because of surgery. Therefore, 21 VLBW infants remained in the analysis. During the EPO period we took care of 30 VLBW infants of whom 2 were excluded from the study because of surgery and 3 because of death prior to discharge. Therefore, 25 patients treated with EPO remained in the final analysis. Comparison of the two study periods showed no significant difference for birthweight or gestational age. The mean weight was 1,187±266 g in the pre-EPO group and 1,219±239 g in the EPO group. Gestational age was 29.6±2.6 weeks in the pre-EPO group and 29.2±2.9 weeks in the EPO group. The female to male ratio was 12/21 in the pre-EPO group and 13/25 in the EPO group.

The average number of blood transfusions (10–12 ml/kg) in the pre-EPO group was 1.7±2.7 and in the EPO group 0.6±1.9 ($P<0.006$). These numbers include all the transfusions that were received since birth to discharge. Of the 25 infants who were treated with EPO, 3 required blood transfusions compared to 9/21 before EPO was introduced ($P<0.05$). The cost of blood products and supplies and the cost of EPO are shown in Table 1. The costs of labor (nursing and /or physician time) involved in the administration of blood vs. EPO were not included in the cost calculation. Also not included in the cost summary is the fact that at times, cytomegalovirus-negative blood was unavailable. In such cases leukocyte filters had to be utilized, adding $33 to the cost of transfusion. The average cost of blood transfusions per infant during the pre-EPO period was US$ 151±189 and during the EPO period US$ 57±87 ($P<0.001$). Thus, the combined cost of blood transfusion and EPO during the EPO period was US$128±168, which is still significantly lower than the US$ 151±189 blood costs of the pre-EPO period ($P<0.01$). No adverse effects were attributable to either blood transfusions or to EPO therapy.

Discussion

Our retrospective study shows a significant reduction in blood transfusions after the introduction of EPO therapy compared to the pre-EPO period. This was not accompanied by an increase in total cost, since the increased cost was largely balanced by the decrease in blood bank charges. Bearing in mind that the risks of transfusions are not negligible, from a pure health standpoint the achievement of our protocol was considerable. It has recently been determined that routine viral screening of donated blood does not completely abolish the risk of transfusion-induced infection. Indeed, the risk of donating blood during an infectious window period have been estimated to be as follows: human immunodeficiency virus 1/40,000 to 1/493,000, human T cell leukemia virus 1/50,000–1/641,000, hepatitis C virus 1/3,300–1/103,000 and hepatitis B virus 1/63,000–1/200,000 [16,17]. There are considerable risks other than infectious ones, such as electrolyte and acid-base imbalances, iron overload, exposure to plasticizers, and alloimmune reactions [16]. Moreover, additional risks specific to preterm infants include increased susceptibility to oxidant damage and increased risk of graft-versus-host reaction [18]. Clearly, any single blood transfusion that can be avoided is of benefit to the patient. There are essentially no significant side effects from EPO;

adverse events occurred at similar rates in patients treated with placebo.

From a cost standpoint, the advantages of EPO were significant. Most prospective studies have shown that the costs of EPO are the same or cheaper than placebo therapy. Our interpretation of these studies is that EPO seemed to be far more efficient when used in higher doses (e.g., 700 units/kg weight/week as compared to 500 units/kg weight/week) [14,15,19]. Also, it appears that the results of EPO therapy are less impressive when it is used early (first week of life), in combination with parenteral iron [18], rather than late. Our study did not include the cost of personnel and workload for either of the treatment modalities, although it may be assumed that the administration of blood requires more personal time (preparation, monitoring, etc.) than the administration of EPO.

The cost of EPO, as well as of most disposable items needed for blood transfusion, has mostly been studied in the USA, where EPO is locally produced. Since blood bank charges and the cost of imported items may vary strikingly in different countries, it was important to conduct such an analysis of cost in our country.

From our study, it appears that the use of EPO at a relatively high dose is both efficient and cost-effective to treat anemia of prematurity in Israel. Calculation of the cost figures presented here was possible due both to the complete use of each ampule and to coordination of EPO administration in a standardized manner.

A limitation of our study resides in its retrospective, non-randomized design. The comparison of two time periods may introduce subtle biases due to the longitudinal changes in routines, laboratory methods, etc. We believe that the uniformity of the two periods with regard to both our blood transfusion policy and laboratory methods renders our results credible. When the major confounding variables (in our case transfusion policy and laboratory methods) are controlled for, the results of a retrospective study, such as ours, rarely disagree to any extent with those of an equally well-conducted prospective study [20].

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