The Use of Erythropoietin for Anemia of Prematurity in North of Jordan, Outcome and Impact on Blood Transfusion

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Abstract

Background: Anemia of prematurity (AOP) is a common problem affecting preterm babies admitted to the neonatal intensive care unit particularly those born with very low birth weight (VLBW <1500 grams). Erythropoietin (EPO) has been recognized as one of the therapeutic options since the 1980's. However, blood transfusion is still used for treating AOP at different thresholds, even in non-emergent situations. In late 2015, we created an EPO initiative for treatment of AOP in our unit at King Abdullah University Hospital.

Objective: To describe the use of EPO in cases of AOP in our VLBW infant population and review its effect on reducing the need for blood transfusion. We also monitored the laboratory response to EPO and evaluated the association with retinopathy of prematurity in babies who received this therapy.

Methods: We conducted a retrospective cohort review of VLBW premature babies with AOP who received EPO during their stay at our unit between October 2015 and October 2016, and compared them with same number of controls. Collected data included demographics, age at EPO initiation, hemoglobin and reticulocyte count pre and post EPO therapy , timing and dosing of EPO, the dose of iron supplement, the need for blood transfusion before and after therapy, and the presence of retinopathy of prematurity (ROP), other comorbidities and mortality.

Results: 36 VLBW babies received EPO during the study period and were compared with 36 control cases. Babies in the EPO group received blood transfusion less frequently than the controls {Median number of transfusions 1 (1, 2) vs 2 (2, 2), p 0.006}. Response to EPO therapy manifests with a surge in reticulocyte count {5 (2, 7.7) vs 1 (1, 1.3), p 0.04}. There was no difference in the risk of high stage ROP between both groups.

Conclusion: EPO is considered a safe therapy for AOP in stable VLBW infants at our unit. We need to establish or adapt and implement a more structured policy to guide us in treatment of AOP with either therapy.

Keywords: EPO, Anemia of Prematurity, Neonates.

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Introduction

The use of EPO in treating AOP remains controversial across the world, many NICU's have adapted its use for decades in the absence of practice guidelines with variable reported effect on blood transfusion, and this has been extensively studied[1,2]. AOP is a common

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problem seen in premature babies particularly those with very low birth weight (VLBW < 1500 grams), its occurrence is related to both physiologic and non-physiologic changes in the first weeks of life. Physiologic changes include the shorter life span of red blood cells in the newborns, lower endogenous EPO level, oxygen sensitivity switch from liver to kidney postnatally and rapid volume growth [3,4]. Non-physiologic changes include the inadequate nutritional intake and coexisting co-morbid illnesses that may cause blood loss like hemorrhage or frequent blood sampling[5]. For AOP, EPO can be given early as a prophylaxis (before the age of 8 days) or late as a therapy for correction of anemia in established cases (after the age of 8 days) [1,2]. The use of EPO aims at minimizing the need for blood transfusion, but results vary between different NICU's and patient population[6]. However, like any other medication, EPO is not without side effects and several studies have focused on the association between EPO and ROP with controversial recommendations.[1,2,7]. Neutropenia was also reported among the side effect of EPO mainly in babies receiving high dose.

In late 2015, we have introduced EPO in our neonatal formulary and we have used it to treat VLBW babies with Hb less than 11 gm/dl. Therefore, we decided to conduct this review to evaluate the outcome of EPO use in our unit and to determine its impact on the clinical outcomes of our babies particularly the frequency of blood transfusion and risk of ROP in our set up.

Methods

We conducted a retrospective cohort review of all VLBW premature babies with AOP who received EPO during their stay between October 2015 and October 2016 at the NICU of King Abdullah University Hospital which is the academic hospital affiliated with Jordan University of Science and Technology (JUST). This study was approved by the Institutional Review Board at JUST. List of the babies who received EPO was extracted from database of electronic medical records at the hospital. Parental consent was waived since this was a retrospective chart review with no direct patient intervention.

For each baby in the EPO group, we selected a control baby that matches in gestational age (GA) and birth weight (Bwt) who was born during the 12 months prior to starting the EPO initiative The groups were labelled as EPO (those who received EPO), and N-EPO (for the controls).

Data collected include demographics, age at EPO initiation, Hb and reticulocyte count (RC) pre and post EPO therapy, EPO dose and duration, dose of iron supplement, the need for blood transfusion before and after therapy, total number of transfusions during hospital stay, the result of eye exam for ROP screening, development of sepsis, presence of patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH) and mortality.

In our unit, we routinely check Hb level weekly. For VLBW babies at the age of 14 to 28 days of life, anemia was defined as any Hb level below 11 gm/dl. EPO is given at a dose of 300 units/kg subcutaneously daily for 10 days [6], babies are supplemented with 4-6 mg/kg/day of elemental iron in the form of ferrous sulfate. We minimize blood sampling during the course to once a week check for electrolytes using 0.5 ml of blood except for cases with clinical changes that require work up for possible sepsis. Hb and RC are checked after the last dose of EPO injection.

The indication of blood transfusion is usually up to the discretion of the attending neonatologist without set guidelines although we have a general agreement to be within the boundaries of the general guidelines followed in other units which mainly depend on the respiratory status and support babies are getting. Once indicated, we give 15 ml/kg of packed red blood cells over 3 to 4 hour period.

VLBW babies have eye exams done for ROP screening based on the universal guidelines for premature babies; that is at 4 weeks after birth or 31-32 weeks postconceptional age whichever comes later [8].

We screen for IVH by getting a head ultrasound (HUS) at 7-10 days of life for the first time or sooner if there is any clinical clue for bleeding. For normal HUS, we repeat the test at 30 and 60 days of life. For abnormal initial HUS, we repeat it in 7-14 days according to the findings.

Regarding enteral feeds, our policy is to start with a 24 cal/oz preterm formula or 22 cal/oz enriched formula (according to availability) on the 2nd or 3rd day of life at 20 ml/kg/day via gavage tube and advance by 20 ml/kg/day daily until reaching 150 ml/kg/day if tolerated. Enteral nutrition will be supplemented with Dextrose 0.2 saline before reaching full volume. Total Parenteral Nutrition (TPN) is not available in our unit and we are in the process of establishing a TPN service.

Statistics

The data were analyzed using SPSS PC for Windows Version 23 (SPSS Inc., Chicago, IL). The data were described using medians and interquartile ranges for nonparametric interval and ordinal data and percentages for nominal data. Mann-Whitney U Test was performed to assess statistical significance for ordinal and nonparametric interval data and Pearson Chi-Square test for nominal data. Statistical significance was set a priori as 0.05 two-tail.

Results

A total of 72 VLBW were included in this cohort study, 36 in each group. There was no statistical difference in birth weight, gestational age and other demographics between both groups (Table 1).

During their stay in the hospital, babies in the EPO group received blood less frequent than the N-EPO group {Median number of transfusion 1 (1,2) vs 2 (2,2), *p* 0.006}. The majority of blood transfusion in the EPO group occurred before the initiation of EPO course; 21 (58%) received at least one transfusion prior to EPO, whereas only 7 (19%) got transfused after therapy.

Table 1. Patient demographics

	EPO (n 36)	N-EPO(n 36)	P value
Gestational Age, wks	29 (28-31)	29.5 (29-32)	0.1
Birth weight, gms	1190 (1128-1338)	1205 (1043-1368)	0.6
Male gender	16 (44%)	18 (50%)	0.4
Singleton	17 (47%)	22 (61%)	0.2
Vaginal delivery	7 (19%)	4 (11%)	0.08

Data described as median (IQR 25,75%) or n(%)

Table 2. Clinical outcomes

	EPO (n 36)	N-EPO(n 36)	P value
Number of transfusion	1 (1,2)	2 (2,2)	0.006
ROP ≥ stage 3	2 (5)	1 (2.8)	0.56
Bevacizumab therapy	2 (5)	1 (2.8)	0.31
IVH ≥ grade 2	8 (22)	6 (17)	0.27
Sepsis	4 (11)	4 (11)	0.5
NEC	0 (0)	0 (0)	---
PVL	3 (8)	1 (2.8)	0.08
BPD	9 (25)	8 (22)	0.1
Discharge Hb	10.4 (10,11.2)	11.7 (10.6,13.2)	0.001
Mortality	0 (0)	0 (0)	---

Data described as median (IQR) or n (%)
ROP: Retinopathy of Prematurity. IVH: Intraventricular Hemorrhage
NEC: Necrotizing enterocolitis, PVL: Periventricular leukomalacia,
BPD: Bronchopulmonary dysplasia

Table 3. Laboratory response to EPO

	Pre EPO (n 36)	Post EPO (n 36)	P value
Hb	10.7 (10.2-11.5)	10.7 (9.5-11.9)	0.7
RC	1 (1-1.3)	5 (2. 7.7)	0.04

Data described as median (IQR)
Hb: Hemoglobin, RC: Reticulocyte count

There was a statistically significant difference in Hb level at discharge between both groups. Table no. 2 shows the clinical outcomes among both groups. In terms of ROP, there was no statistical difference of having high stage ROP (stage 3 or more) between both groups. 2/36 babies in the EPO group developed high stage ROP (One baby had stage 3 and one had stage 4) compared with 1/36 in the N-EPO group who had stage 3 (*p* 0.56). ROP regression was noticed in all three affected babies after receiving bevacizumab injection [9]. The two babies with ROP in the EPO group started therapy at 20 and 42 days respectively. None of the babies in EPO group had an absolute neutrophil count less than 1250 after therapy.

Table 3 shows the laboratory response to EPO. There was a surge in RC in the EPO group at the end of the course, {5 (2, 7.7) vs 1 (1, 1.3), *p* 0.04} with minor elevation in Hb level.

Discussion

After one year of EPO initiative at the NICU at KAUH, the use of EPO for treatment of AOP among our VLBW babies was associated with lower number of blood transfusions, but did not totally eliminate the need for transfusion, without any significant complication.

In our VLBW population and during their stay in the hospital, babies in the EPO group received blood less frequent than the N-EPO group; this difference is of significant clinical

and statistical importance. The existent controversial impact of EPO on reducing transfusion requirements in different practices might be attributable to a variety of reasons, including phlebotomy losses that exceeded baby's ability to maintain an adequate Hb level, different threshold for transfusion in the absence of written guidelines, and variable EPO dosing schedule.[10] To avoid any selection bias, the success of EPO on reducing blood transfusion needs to be assessed in the presence of set guidelines for transfusion.

Our finding of reduced frequency of blood transfusion is consistent with the Cochrane meta-analysis conducted in 2014 where Aher et al[1] reported that late EPO use (after the age of 8 days) minimized the number of transfusions, and the number of donors. Prior to that analysis, in 2012 Ohlsson et al[2] reported same benefit among early EPO users (before the age of 8 days) in addition to reduction in the volume of transfusions. Both studies, however, reported higher incidence of ROP among babies who received EPO. Similar beneficial findings were also reported by Lopez et al from France [11], they have not commented on the risk of ROP in their study.

In 2013, Ohls et al [12] conducted a randomized controlled trial using an erythropoiesis stimulating agent (ESA) as EPO or Darbepoietin (A long acting ESA) and found that ESA recipients received fewer transfusions with fewer donor exposures compared with the placebo group. There was no difference in ROP development between the interventional group and the placebo.

The universal trend nowadays is to minimize or eliminate the use of blood transfusions in the NICU's, many NICU's have implemented local guidelines or quality improvement initiatives to prevent unnecessary blood transfusions among premature babies[13,14]. Prior to EPO initiative, the practice in our unit was a liberal use of blood transfusion. Despite all the screening and safety measures followed in blood banks, blood transfusion carries a burden of social, financial and long term effects that should be also considered.

The laboratory response to EPO was assessed in our study by checking Hb and RC after the last dose of EPO therapy. Our babies responded by a surge in RC before the increase in Hb. This finding is a reflection of bone marrow over activity, which explains the mechanism of action of EPO and other ESA[15]. Our finding is consistent with what has been reported by Ohls 2013 in a randomized masked study. We found a better response with higher RC in babies receiving higher dose of Iron supplement at 6 mg/kg/day. Previous neonatal studies evaluated the use of both enteral and parenteral iron in a wide dosing range and noted more reduction in blood transfusion[16], and less chance of developing iron deficiency anemia [17] in recipients of high iron dose.

The possible association between EPO therapy and the development of ROP continues to be a major factor for restricting the use of this therapeutic option in treating AOP in many NICU's. Kandasamy et al in 2014[7] concluded that EPO increases the risk of development and causes worsening of ROP. The Cochrane meta-analysis [1,2] concluded that early and late use of EPO might be associated with increased risk of high stage ROP. In a recent meta-analysis in 2016, Chou et al[18] concluded that EPO administration did not significantly increase the risk of ROP, a similar result was also reported in another meta-analysis in 2014.[19]

In our study, the incidence of high stage ROP was 4% and we have not seen any trend of having higher incidence or high stage of ROP among the EPO group.

This review was not without limitations. One of the limitations is the low number of participants that did not provide a sufficient power to statistically detect the clinically important difference in some of the outcomes. Additionally, this was a retrospective study that involved the review of medical records in the absence of written guidelines regarding the management of AOP with blood transfusion or EPO therapy, so personal bias and different thresholds for blood transfusion could have contributed to the choice of therapy.

Conclusion

EPO use among VLBW in our unit seems to be safe. We might speculate that EPO should not be initiated in these babies before the age of 3 weeks, we proposed 3 weeks as the cutoff age to avoid high stage ROP. To get a better response, a supplement with Iron sulfate at a dose of at least 6 mg/kg/day is recommended.

In order to achieve an optimal care with more consistency and standardization, our future goal is to focus on establishing a written policy for treatment of AOP including guidelines for blood transfusion and indications for EPO therapy at different hemoglobin levels. Further studies to determine the effectiveness of EPO in reducing the frequency of blood transfusion need to be carried out following implementing those policies.

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استخدام الإريثروبويتين لعلاج فقر الدم عند أطفال الخداج في شمال الأردن، النتيجة والأثر على نقل الدم

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الملخص

يعد فقر الدم المصاحب للأطفال الخدّج من المشاكل الشائعة، وقد لوحظت فاعلية استخدام هرمون الاريثروبيوتين (EPO)كخيار علاجي بدلاً من نقل الدم للأطفال الخدّج. علماً بأن نقل الدم ما زال خياراً رئيساً في وحدات الخداج حتى في الحالات غير الحرجة. في نهايات عام 2015م بادرنا باستخدام الاريثروبيوتين في قسم الخداج في مستشفى الملك المؤسس عبدالله الجامعي لعلاج فقر الدم.

الهدف: تحديد مدى فاعلية الاريثروبيوتين في علاج فقر الدم المصاحب للأطفال الخدّج، وذلك للحد من نقل الدم إليهم اعتماداً على نتائج الفحوصات المخبرية. ودراسة العلاقة بين استخدامه واحتمالية الإصابة باعتلال الشبكية للأطفال الخدّج.

الطريقة: لقد أجرينا دراسة استعادية (بشكل رجعي) للأطفال الخدّج الذين يعانون من فقر الدم، الذين تلقوا هرمون الاريثروبيوتين في الفترة ما بين 2015م-2016م. وقارناهم مع مجموعة أخرى من نفس العدد، مطابقين لهم من حيث العمر الحملي ووزن الولادة، ولكن تم نقل الدم إليهم عوضاً عن استخدام الاريثروبيوتين.

النتائج: تم مقارنة (المجموعة الأولى) 36 رضيع خداج ممن تلقوا الاريثروبيوتين، مع (المجموعة الثانية) 36 رضيع خداج الذين تم نقل الدم إليهم عوضا عن استخدام الاريثروبيوتين.

المتوسط الحسابي 1 (2,1) مقابل 2 (2,2) (p 0.006).

وتبين أنه قد تم نقل الدم للمجموعة الأولى بشكل أقل من المجموعة الثانية. وأنه لا يوجد فرق في احتمالية التعرض للاعتلال الشبكي الحاد بين المجموعتين.

الخلاصة: يعد الاريثروبيوتين بديلاً آمناً لنقل الدم لدى الأطفال الخدّج الذين تقل أو تساوي أوزانهم 1500 جرام في وحدة الخداج الخاصة بنا في مستشفى الملك المؤسس عبد الله الجامعي. وجارٍ العمل على وضع أسس واضحة لعلاج فقر الدم لدى الأطفال الخدّج حسب الحالة والمعطيات.

الكلمات الدالة: الاريثروبويتين، فقر الدم، الأطفال الخدج.