

Comparison of Oral and Injection Erythropoietin on Level of Hemoglobin Concentration in Premature Neonates: Randomized Clinical Trials

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ABSTRACT: Preterm infants, often develop anemia which need for transfusion. Erythropoietin is effective in decreasing the number of transfusion needed in these infants. The aim of current study is to compare the efficacy of oral and injection erythropoietin in preterm neonates. Method: In a randomized controlled trial, 38 low birth weight (LBW) infants with gestational age ≤ 34 weeks who met the inclusion criteria and did not have exclusion criteria were selected. Neonates were divided in two groups of case and control. Control group received 250 μ /kg subcutaneous erythropoietin, three times a week and the case group received 1000 u/kg of oral erythropoietin three times a week. The two group were compared for the number of transfusion, hemoglobin, and hematocrit level in first, second, third and fourth week of study. Data was analyzed via SPSS® ver. 16 for Windows®. The two groups were similar in baseline characteristics. There were no significant difference between two groups in the number of transfusion ($p=0.37$); there were no significant different in quantity of hemoglobin in weeks one to four of study, between two groups ($p>0.05$). The mean basic Hemoglobin in the control was 10.52 ± 2.4 and $11, 13 \pm 2.3$ in case. At the fourth week, mean Hemoglobin was 8.73 ± 1.12 in control and 8.89 ± 1.6 in case. The mean basic hematocrit was 30.73 ± 6.69 in control and 32.67 ± 6.63 in case, and at the fourth week it was 26.84 ± 3.66 in control and 26.64 ± 4.7 in case. There were no significant difference between mean Hemoglobin and mean hematocrit in the beginning and week one to four. The reticulocyte count increases from 1.9 to 2.4 at the end if study. Oral and subcutaneous erythropoietin have similar effect; oral erythropoietin is less intensive and this method is suggested in the treatment of anemia of prematurity.

Keywords: Anemia of prematurity, Erythropoietin, Transfusion

ORIGINAL ARTICLE

INTRODUCTION

In response of hypoxia, Erythropoietin is produced by hepatic cells and renal cortex interstitial cells by effect of Hypoxia Inducible Factor 1. It primarily adjusts production of erythrocytes. Human erythropoietin does not pass the placenta and its fetal production increases by age. (Malek et al., 1994; Schneider et al., 1995; Widness et al., 1995; Palis et al., 1998) in anemia of prematurity, mechanisms which disturb serum Erythropoietin concentration and severity of anemia is unknown. Erythropoietin production site and liver and kidney regulatory factor can affect Erythropoietin concentration and severity of anemia. (Moritz et al., 1997; Dame et al., 1998). Liver is primary site of Erythropoietin production in fetus. In response to anemia and hypoxia, increase in liver erythropoietin may be less than that of kidney. (Tan et al., 1992) erythropoietin mRNA expression in the kidney is present in the fetus, and increases significantly after 30 weeks gestation, suggesting that the switch to the kidney

as the main site of erythropoietin production. Anemia of prematurity typically occurs in 3 to 12 week of age in infants less than 32 weeks gestation. Onset of anemia of prematurity relates inversely with gestational age (Ohls et al., 2000; Stockman Anemia usually resolve in 3 to 6 month of age. In a study on 40 neonate with very low birth weight (VLBW), showed that t et al., 1984; Stockman et al 1977). Hemoglobin level fell from 18.2 g/dL at birth to a low of 9.5 ± 1.5 g/dL at 6 weeks of age. (Stockman et al., 1980). levels of 7-8 g/dl was common in the absent of significant phlebotomy. Levels of hematocrit in low birth weight were lower; 21% in neonates less than 1000 g and 24% in neonates between 1000 to 1500 g.

Some infants can be asymptomatic despite having hemoglobin levels > 7 g/dL. However, other infants can become symptomatic at similar or even higher hemoglobin levels due to increased requirement of supplemental oxygen, or increased frequency of apnea or bradycardia. Although anemia of prematurity is directly due to

impaired Erythropoietin production, several other factors can contribute to anemia in preterm infants, including: 1- Blood loss due to phlebotomy for blood tests; the volume of blood loss increases with illness severity and decreasing gestational age. In one study, withdrawal of blood in excess of that required for laboratory tests contributed to blood loss by 2 to 4 mL/kg per week. 2- reduced red blood cell (RBC) life span; RBCs have average time life of 60 to 80 days in infant but in neonates with VLBW is of 45 to 50 days (KAPLAN, 1961). The reduced red cell life span is related to the severity of anemia. Increased susceptibility to oxidant injury may contribute to shortened RBC time life. (Shahal et al., 1991; Robles et al., 2001). 3-Iron deficiency; Because of their rapid growth rate and frequent phlebotomy premature infants have increased need to iron. The administration of iron inhibits fall of Hemoglobin in anemia of prematurity. (Stockman et al., 1984) Low levels of vitamin B12 or folate, do not appear to contribute to neonatal anemia (Ohls, 2000) In one clinical trial, the combination of folate, vitamin B12, iron, and Erythropoietin compared to control therapy improved the VLBW infant's chance of remaining transfusion free (38 versus 5 percent). (Haiden et al., 2006).

The pathologic importance of erythropoietin impairment in anemia of prematurity, contributes need for recombinants human erythropoietin. Because of its inability to decrease the numbers of transfusion, whether with early (within one week) or late (after 8 days administration of erythropoietin), this approach is not accepted widely. A more effective method to lessen the number of transfusion in routine erythropoietin administration is to limit the amount of blood drawn, follow restrictive guidelines for red blood cell transfusion, and to use satellite packs (Birenbaum et al., 2006) in retrospective studies early administration of erythropoietin was associated with slightly decrease in number of transfusion but increased the risk of retinopathy of prematurity. In addition, erythropoietin is an expensive intervention. As a result, routine use of erythropoietin in neonates is not recommended, because it's cost and potential risks exceed its potential benefit. Even so meta-analysis has shown the risk of retinopathy of prematurity, it can be an accidental finding because retinopathy is thought to be a secondary outcome (Ohlsson et al., 2006). Also there were no differences between the erythropoietin and placebo groups in the rates of mortality, sepsis, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, hypertension, length of hospital stay, or long-term neurodevelopmental outcomes.

Late administration of erythropoietin reduced number of transfusions but its limited benefits does not justify that. This was illustrated in a meta-analysis of 28 trials (1302 preterm infants) which evaluated the effects of

late erythropoietin administration (at or later than eight days of age) compared to placebo (Aher et al., 2006). Most of these infants had blood transfusions prior to enrollment in the trials. Results were found: erythropoietin reduced the risk of receiving one or more red blood cell transfusions as well as the number of red blood cell transfusions and had no effect on the rates for retinopathy of prematurity, mortality, sepsis, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, hypertension, length of hospital stay, or long-term neurodevelopmental outcomes.

In another trail by Ohls (2000) a combination of erythropoietin and parenteral iron in neonates less than 750 g induced erythropoiesis and lessened the numbers of transfusion. Currently parenteral erythropoietin is recommended. By considering a very thin skin of premature neonates, to discover a non- invasive method we carry on this study to compare the effect of oral erythropoietin by parenteral erythropoietin in Hemoglobin concentration in premature neonates.

METHODS AND MATERIALS

This study was a randomized clinical trial and the population was premature neonates in neonatal ward and NICU in Bandar-e-Abbas children hospital in 2011. 20 premature neonates were divided randomly in each group. Inclusion criteria were premature neonate with gestational age >34 weeks, weighting > 1500 g, an hematocrit > 40% in 7th day of birth who could fed orally (at least 100cc/kg per day). Exclusion criteria were intracranial hemorrhage and gastrointestinal bleeding or any source of internal or external bleeding, diarrhea, vomiting, and any kind of dyspepsia, fatal anomalies, Glucose-6-phosphat dehydrogenase deficiency and ABO incompatibility. After having consent, neonates were divided in case and control group. After second week, considering the ability of oral feeding, control group received subcutaneous erythropoietin 250 U/kg divided in 3 does, 3 times a week for four weeks. The cases received oral erythropoietin 1000 U/kg, 3 times a week. Erythropoietin was supplied by Pooyesh-Daroo pharmaceutical in oral or injection 2000 U vial. In both group 4mg/kg of oral iron daily was administrated with erythropoietin. In both group Hemoglobin, hematocrit, Reticulocytes, mother and neonate blood group, G6PD, brain ultrasonography and peripheral blood smear was evaluated before administration of erythropoietin. Hemoglobin, hematocrit, Reticulocytes was measured at the beginning and week one, two and tree and at the end of trial. Demographic information including age, sex, Hemoglobin, hematocrit, gestational age, weight, numbers of transfusion, and rout of erythropoietin administration was collected by pediatric residents. Data was analyzed via SPSS® 16 for windows ®.

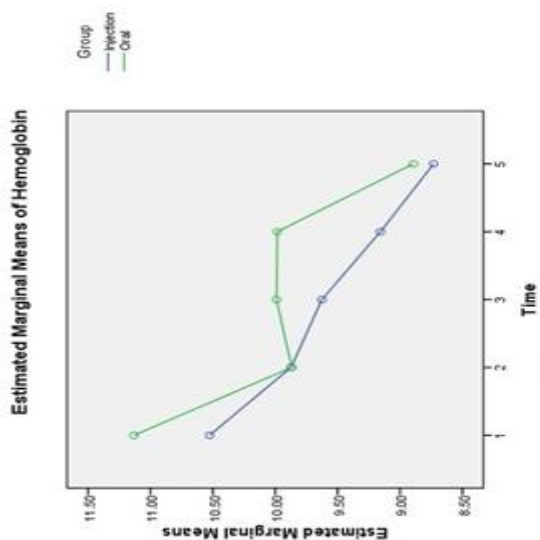


Figure 1. Comparison of Hb during time between oral and injection

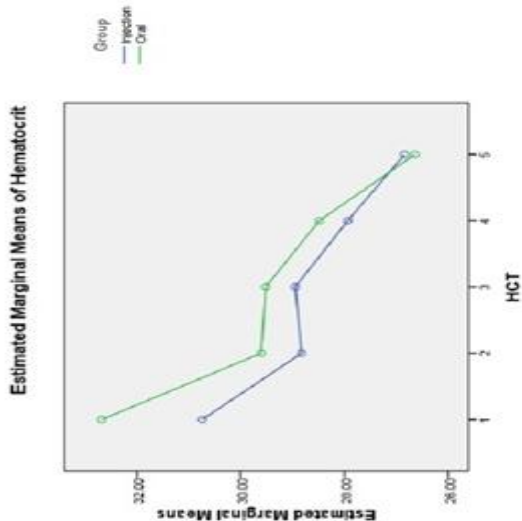


Figure 2. Comparison of mean HCT in 5 time measurements

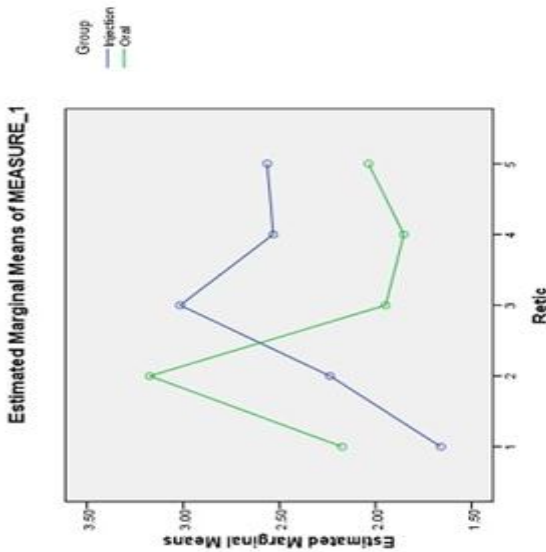


Figure 3. Comparison of Reticulocyte count in 5 time measurements

RESULTS

38 neonates were enrolled. Of which 19 (50%) put for injection group and 19 (50%) for oral group. In injection group, 10 (52.6 %) were male and in oral group 9 (47.4%) were male. This difference was not significant ($p=0.500$).

In injection group 6 (31.6%) and 4 (21.1%) in oral group were twins. This difference was not significant ($p=0.753$). Mean maternal age in injection group was 30.05 ± 2.29 and in oral group was 28.78 ± 1.54 . Mean gestational age was 30.05 ± 2.29 weeks in injection group and 28.78 ± 1.54 weeks in oral group. Which all were almost similar in both groups.

As seen in table 1, according to the chi-square testing there was no statistically significant difference in numbers of transfusion between two groups. Table 3 demonstrates there were no significant difference between basic and week one to four HCT ($p>0.05$).

In general, with 5 times measuring, total Hb fell in both group from 10.8g/dl to 8.8g/dl ($p<0.001$, $F=8.519$, $DF=2.96$).

According to figure 1, this fall was almost similar and has a same regression in both groups. According to Greenhouse-Geisser approach, there was generally a significant difference between mean HCT in 5 time measurements. ($P<0.001$, $F=9.004$, $DF=2.63$). According to figure 2, generally effectiveness of each method was proximally similar and with same progress. As seen in figure3, after 5 times measuring, Reticulocyte count has increased from 1.9 to 2.4. According to Greenhouse-Geisser, this was not a significant difference ($P=0.079$, $F=2.43$, $DF=2.568$), but there was a significant decrease in both group. ($P=0.005$, $F=4.6$, $df=2.56$).

DISCUSSION

From 38 neonates, 19 (50%) put for injection group and 19 (50%) for oral group. In injection group, 10 (52.6 %) were male and in oral group 9 (47.4%) were male. This difference was not significant ($p=0.500$).

Although studies have shown the benefit of EPO for treatment of AOP, there are no standard guidelines.⁸⁻⁹ Experts say that establishing a guideline for treating AOP by EPO is impossible or rather difficult; which shows the importance of study.

There are not many studies in different rout of administration for EPO, and most of them have focused on dosage and number of administration.

Our study showed that there are not difference in Hb, HCT, and the need for transfusion at the beginning and week one to four, between two groups. Rocha and colleagues also did not showed a difference in the need for transfusion, between daily and twice a week treatment with EPO. Brown and colleagues did not showed the

difference in need for transfusion between treatment with 2 doses and 5 doses of EPO in week, either.

Although result of many studies indicate the benefit of treatment of EPO for AOP, considering limited ones for

comparing difference method of administration, extensive study to find a method of choosing seem reasonable. Considering our limitation on population size, we suggest feature studies on larger population.

Table 1. Comparison numbers of transfusion in injection and oral groups

	No transfusion	One transfusion	Multi-transfusion	P-value
Injection I group	10(54.4%)	6(60%)	3(50%)	0.748
Oral group	12(54.5%)	4(40%)	3(50%)	

Table 2. Comparison between basic and week one to four Hb concentration

	Injection group	Oral group	P-value
Basic Hb	10.52±2.41	11.12±2.32	0.436
Week one	9.87±2.03	9.86±1.84	0.993
Week two	9.62±1.43	9.98±1.92	0.514
Week three	9.15±0.92	9.98±2.61	0.202
Week four	8.73±1.12	8.89±1.64	0.732

Table 3. Comparison between basic and week one to four HCT concentration

	Injection group	Oral group	P-value
Basic HCT	30.73±6.69	32.67±6.63	0.376
Week one	28.82±5.65	29.60±5.24	0.662
Week two	28.94±3.60	29.51±5.58	0.712
Week three	27.93±3.35	28.48±5.37	0.709
Week four	26.84±3.66	26.64±4.70	0.885

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