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Recent Understanding of Erythropoietin and Retinopathy of prematurity

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Abstract
Erythropoietin (EPO) is a glycoprotein hormone which is produced by specialized cells in the kidney that induces hematopoietic stem cells of bone marrow and controls erythropoiesis. It acts in proliferative diabetic retinopathy independently of vascular endothelial growth factor as retinal angiogenesis. Retinopathy of prematurity (ROP) is a serious disease associated with the vasoproliferative disorder which becomes clinically important mainly in extremely premature infant. ROP is considered one of the leading preventable vision threatening disorders among low birth weight babies worldwide. As pre-term infants usually have been treated with erythropoietin for prevention of anemia so they are at greater risk for development of retinopathy of prematurity. Presently about 10% of births occur pre-term worldwide. Regarding the pathogenesis of ROP most of them are based on animal model so, the research findings are not 100% applicable to humans. Before reports suggest that treatment with EPO increase the risk factor of ROP. Some observation reports that development of ROP would be affected by dose, timing and administration of EPO. Meanwhile, some reports suggest statistical significance that EPO is one of the independent risk factor. Some recent study have come with the relationship between EPO and ROP .Growing body of evidences focus that pre-term are at increased risk of severe ROP. However, studies focusing on effect of EPO on ROP over time have painted an inconsistent picture. We have tried to integrate the studies, which have been done in past and present, to identify the relationship between EPO and ROP.
Keywords: Retinopathy of prematurity, erythropoietin, dose, relationship, low birth weight, retinal angiogenesis.

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Introduction

Erythropoietin

Erythropoietin is a glycoprotein hormone which is produced by specialized cells in the kidney that stimulates hematopoietic stem cells of bone marrow and controls erythropoiesis (production of red blood cell). Erythropoietin is produced by the liver during fetal life and after birth, the kidneys constitute the major source of production. Erythropoietin, a member of class 1 cytokines, is a 30.4-kDa glycoprotein which is formed with carbohydrate and protein chain contain of 193 amino acids which goes under cleavage process and results in production of mature erythropoietin. These cells possess specific regulatory mechanisms called hypoxia-inducible factors (HIFs) which under hypoxic conditions stimulate the production of erythropoietin, which stimulates the production of erythrocytes [1].

EPO is known mainly for hematopoiesis and it has been used to treat anemia. However, increasing evidence indicates that EPO has other biological effects, including neuroprotective, antiapoptotic [2] and angiogenic [3, 4] properties. In the brain, rEpo decreases neuronal apoptosis, oxidative injury [5-11], excitotoxicity [7, 8] , and inflammation. In particular, the possible *in vivo* role of recombinant human erythropoietin (EPO) in promoting angiogenesis and ultimately ROP has been underlined by some recent studies [12, 13]. Erythropoietin is a factor inducing retinal angiogenesis in proliferative diabetic retinopathy independently of VEGF. Moreover, it is known that hematopoietic and endothelial cell lineages share common progenitors and some cytokines formerly thought to be specific for the hematopoietic system, have recently shown to affect several functions in endothelial cells, including angiogenesis [14, 15]. Both EPO and VEGF are dependent of oxygen concentrations which are regulated by hypoxia inducible factor-1α stabilization [15, 16].

EPO is necessary for growth of normal retina, it is due to presence of EPO receptor in the region of active cell reproduction in the growing retina which is mediated by over expression , that may be due to hypoxia or ischemia events in the retina [15].

Retinopathy of Prematurity

In the early 1940s, retinopathy of prematurity appeared in premature babies [17]. Later in 1942, it was first reported the end stage of the disease and named as retrolental fibroplasia, but advancement in study renamed it as ROP (Retinopathy of

prematurity). Retinopathy of prematurity (ROP) is a serious disease associated with the vasoproliferative disorder that affects mainly extremely premature infants. ROP is considered one of the leading preventable vision threatening disorders among low birth weight babies worldwide. As pathophysiology of ROP remains poorly understood, but still low birth weight and pre-term delivery are well known risk factors which are inversely related to the progression of ROP [18-20]. When premature infants are born the normal retinal vascular maturation is impaired. On exposure of vascular endothelial growth factor (VEGF) leads to constriction of retinal blood vessels impairing the retinal blood vessels formations. As a result hyperoxia conditions associated with vasoconstriction of retinal blood vessels which leads to ROP [4]. Its pathogenesis is multi-factorial, but the amount of oxygen saturation in pre-term infant is the important factor. The pathogenesis of ROP is more complex than the VEGF theory but both fetal and maternal factors play a role [21].

Apart from above mentioned risk factors of ROP, there are many more causes that can leads to ROP including mechanical ventilation, episodes of blood transfusions, apnea, episodes of hypoxemia, hypercarbia, and hypocarbia [22]. But few studies found that there was significant association in progression of ROP when EPO was given to premature infants [23-25]. As rhEPO is routinely used for managing anemia of prematurity in NICUs, some of the basic factor may be playing a basic role in determining ROP (e.g., the number of blood transfusions, cumulative dose, and timing of erythropoietin treatment [26-28] . Still some of studies based on this did not find link between administration of EPO and ROP progression [29, 30]. Severe stage of ROP can lead to lifelong disabilities for the smallest survivors. So, improved understanding of the ROP disease and improvement of new screening protocols to predict ROP much earlier with the possibility of new preventative treatments are highly desirable.

Prevalence

Presently about 10% pre-term births occurs worldwide (before 37 weeks of gestational age) which is most common cause of neonatal death. Prevalence of ROP has been surveyed in most countries. It was reported that the prevalence of ROP was 15.6% in the USA [31], 36.1% in Germany[32], 36.4% in Sweden [19] and 29.2% in Singapore [18]. As the difference in the prevalence of ROP seen in these countries suggests that some of the factors influencing the incidence of ROP such as the race, geographical region, economic development of country and degree of social and medical development. Prevalence of ROP in china was surveyed in Shanghai and Beijing [33] . As these are highly developed cities so the data fails about exact prevalence of ROP in china. As ROP is seen in pre-term and smaller infants, the countries which have low income and which are in urban areas where neonatal care is improving rapidly can help to decrease the rate of ROP blindness [34].

China itself is a middle income country and has significant advancement in neonate management and as latest methods of mechanical ventilation and frequent use of surfactant therapy helped a lot to improve the survival rates of pre-term infants but still facing the increasing number of ROP. Hence it is referred as “third epidemic” of ROP. In China, many studies which suggest incidence of ROP is lower in highly developed regions but still some of study in past suggest ROP is becoming an important cause of blindness in China [35] .

Dose of rhEPO

Till date many of the researchers still belief the development of ROP would be affected by dose, timing and administration of EPO. In past study of Romagnoli et al.[23] mean total dose administrated was 5400 IU/kg from the 2nd to the 7th week of life in the case group meanwhile iron was supplied by orally or intravenously, total dose of 266 mg/kg was used in whole process of management, in which, normal group of infant did not receive rhEPO or iron .Suk et al.[13] reported that ROP increases among pre-term who had received >20 doses of rhEPO was higher compared with those who received < or =20 doses (OR 3.53; 95% CI, 1.59, 7.85), however the doses of rhEPO found to be significant predictor of the severity of ROP with higher doses having significant role in inducing risk of severe ROP (OR4.31).

A Cochrane systematic review, done in past to determine late EPO administration for preventing red blood transfusion in premature infants which resulted in no association with ROP, and it’s any stage [36]. Whereas in the same year another review assessed early EPO for prevention of red blood transfusion in premature infants .They found there was no relation with all stages of ROP but was significantly related

with severe stage ≥3 ROP(OR 1.17, 95 % CI 0.98–1.39) [37].

Another Cochrane systematic review [37] which had include two studies and meta-analysis comparison between early and late (0–7 days, 8–28 days) supplement of EPO for prevention of transfusion in premature neonates which showed greater incidence of ROP [typical RR 1.40 (95 % CI 1.05 to 1.86); typical RD 0.16 (95 % CI 0.03–0.29); number needed to harm; 6 (95 % CI 3–33). Although this all needs to be tested in higher studies. More recently, in the meta-analysis study done by Xu-Juan Xu [38] and team in their study which was conducted into two groups that was related to time and dose of EPO administration(higher dose and lower dose) which was varied from 100– 1,200 IU/kg. They concluded, there was no relationship in administration of EPO with any stage of ROP including stage ≥3 severe ROP, same as one of the Cochrane systematic review discussed above. Researcher of this study also conclude that dose and timing of EPO need to be confirmed by further high-quality studies.

But some of the animals study has conform about the extreme doses of EPO does not exacerbate retinopathy of prematurity in rats [39]. The dose of EPO which is given to pre-term infants is to determine the importance and decrease need of blood transmission but till now dose of rhEPO on ROP is still controversy.

Effect of rhEPO on ROP

The function of EPO is erythrocyte maturation and differentiation as EPO in fetal is produced by liver after that in adult by kidney, some investigation showed the role of EPO in migration of endothelial progenitor cells and angiogenesis [12]. More recent studies showed the effect of EPO other than stimulation of erythropoiesis in bone marrow [40, 41]. Lubetzky et al [42] reported that neonates who received more number of red blood cell transfusion were more likely to develop ROP due to increase in erythropoiesis, in compare to neonates who receive less number of transfusion. Meanwhile, Watanabe et al. studied EPO level in adult case group of proliferative diabetic retinopathy in which they found case group statically significant as compare to control group and hence proposed that EPO is a potent ischemia-induced angiogenic factor which directly acts on VEGF during retinal angiogenesis in proliferative diabetic retinopathy [43]. Later, Patel et al [44] Proposed that there is possible changes in EPO production after the birth of preterm baby which may affect retinal vascularization .In fetal retina, EPO mRNA increases with increasing gestational age ,Somehow concentrations of EPO are significantly higher which is maintained throughout pregnancy. Later ,Chen and smith [45] study demonstrated EPO as double-edged sword in eyes with retinopathy of prematurity. According to him ROP can be prevented at the time of administer of rhEPO that induce angiogenesis and inhibit retinal vasculature in the early stage when low IGF-1 levels prevent the angiogenic effect of VEGF [46].

In past systematic review by Asher and Ohlsson [37] , pre-term receiving rHuEPO compare to that who received EPO less than eight postnatal days led to higher risk of ROP. To make it more clear some of the studies found the increasing risk of ROP was relatively higher who got rhEPO >20 days .But till date it is unclear whether it is dependent on EPO dose or not. Recently, Y Kandasamy et al [47], a retrospective review studies, which was done to determine the severity of ROP associated with various risk factors. They also concluded that use of EPO have significant association in increasing number of ROP (P=0.004). However the study fails to show dose-response relationship. In the study cumulative dose of EPO received by preterm with mild ROP was more than those who had severe ROP. Hence, to establish erythropoietin as a contributory cause, it is important for the cause to not only have statistical significance but also alter the effect on altering the cause.

Relationship between EPO and ROP

During the time, NICUs and many health institutes started using recombinant human erythropoietin. Presently, recombinant human erythropoietin (rhEPO) is being used as transfusion therapy in premature neonates which is generally synthesized by recombinant DNA technique [23]. Over the time, we have seen in both human clinical trials [48, 49] and animal studies [50, 51] recombinant human erythropoietin (rhEPO) have been significantly used to reduced risk of perinatal asphyxia, in management of periventricular leukomalacia, [48] and in reducing time of mechanical ventilation in premature infants[52]. In context of ROP some of the intense research with human data and animals studies are showing finding of linking between rHuEPO with ROP [53]. As recombinant EPO is being used to decrease the rate of anemia of pre-maturity, indeed

many researcher have indicated that there is relation between uses of EPO which leads to severity of ROP.

Many researchers have compared the use of human erythropoietin and iron supplement between infants who haven't developed ROP, they found that the rate of retinopathy of prematurity was much higher in the group who were treated. They also proposed that supplementation of iron would increase some of the free iron level in retina which adds to oxidative injury of the retinal vessels. But they failed to show the blood transfusion management of control group in compare to case group [54, 55]. Meanwhile, research performed in two different centers in USA, on using EPO for anemia of prematurity, total dose administered was 100 UI/kg 5 days a week used for ≥35 weeks gestational age (which is about the time when the vasoproliferation phase of ROP begins to appear), neither one showed greater incidence of ROP in EPO-treated infants [56-58]. Later, study of Chen et al. also contributed that use of EPO in early phase of retinopathy may prevent damaging retinal neovascularization and treating in late phase of neovascularization it may exacerbate the disease due to endothelial cell proliferation [33].

In previous studies, Romagnoli et al. [23] study they found that incidence of stage 3 ROP was statistically significant in the case group compared to control group which was 17.4% and 7.8% respectively, from which they conclude that ,iron supplement may be the contributing factor. Later again Romagnoli et al. [59] in 2013 worked on administration of early EPO between intravenous and subcutaneous route and they found the incidence of stage 3 ROP was 16% in intravenous and 14% in subcutaneous group. This incidence was very close to their previous study. Many of the non-randomized studies support an association between early EPO and ROP. Such as Brown et al. [56] found administration of total six week dose was independently associated with progression of ROP. Recently, P. Manzoni et al [60], on multivariate logistic regression, they found many risk factors associated with progression of ROP but attention was drawn to EPO which was independently and significantly associated with the development of the most severe stages of ROP in preterm infants ($p = 0.009$). All the above mentioned study was retrospective in nature and it gives clear view of early EPO administration and progression of ROP. In latest published Cochrane systematic review, they concluded administration of rhEPO in early phase leads in significant increase in stage 3 ROP and stage≥3, but delay in administration also did not change any incidence of ROP [61]. They also observe in animal model and other studies revels a possible link between management with EPO and progression of ROP.

Conclusion

Erythropoietin is a glycoprotein hormone which controls red blood cell production. It also acts in proliferative diabetic retinopathy independently of vascular endothelial growth factor as retinal angiogenesis. It has been used to reduce transfusions in premature infants in NICUs. All the research till date haven't clearly understood the mechanism of EPO in relation to ROP. In past and recently all the studies point that there is significant relation between administration of rhEPO and ROP in premature infant. Additionally, there are controversial results about the relationship between rhEPO treatments and the incidence and severity of ROP. Larger population-based, controlled studies should be designed to validate the efficacy and safety of the administration of EPO in pre-term infants. Studies should be focused on how to decease blood transfusion in first week of life, when there is need for red blood transfusion find other means or use of satellite packs in combination with late EPO management. So, further we can clarify and extend the association for improving the outcome in premature infants who undergoes treatment of EPO.
In the meantime EPO therapy increases the risk of development and tends to worsening ROP.

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