The Netherlands retinopathy of prematurity study

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Chapter 7

Letter to the editor

Severe retinopathy of prematurity in twin–twin transfusion syndrome after multiple blood transfusions

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Retinopathy of Prematurity (ROP) is a potentially blinding disease in premature infants. Several risk factors associated with the development of ROP have been reported such as gestational age (GA), birth weight (BW), duration of artificial ventilation, sepsis and blood transfusions, whereas prenatal glucocorticoids would be protective. Vascularisation of the retina starts at 16 weeks and is completed around 40 weeks of gestation. Outgrowth of vessels is defined in 3 Zones, Zone I being the most central one.[1] Vascular Endothelial Growth factor (VEGF) and Insuline-like Growth Factor-1 (IGF-1), produced by the placenta, play a crucial role in vascularisation of the retina.[2] ROP is defined as abnormal vessel growth in the developing retina. In the first phase of ROP down regulation of VEGF together with a decrease of IGF-1 causes an arrest in vessel outgrowth. In the second phase of ROP IGF-1 levels slowly and VEGF-levels more rapidly increase causing plus disease (tortuosity and dilation of retinal vessels) and neovascularizations. Twin-Twin Transfusion Syndrome (TTTS) complicates 10-15% of monochorionic diamniotic twin pregnancies. This is a second report of TTTS accompanied by severe ROP and describes the history of two twins.[4] GA, BW, risk factors and specifications about ROP are presented in table 1. Both donor twins showed normal weight gain and catch-up growth. The course of development of ROP was remarkable as it developed rapidly although the outgrowth of retinal vessels had already progressed to peripheral zone II. In the first donor twin ROP stage 1 without plus disease was seen up to 39 weeks Post Menstrual Age (PMA) then rapidly progressing to stage 5. The second donor twin presented with stage 3 ROP with plus disease at the first examination.

Multiple births are unique because of the confounding effect of certain risk factors, such as GA and maternal risk factors, on incidence and severity of ROP. Both donor twins had several mild risk factors for ROP. The most striking difference between the donor and the recipient twins however is the number of blood transfusions given within 3 weeks postnatal age.

Red blood cell (RBC) transfusions are associated with an increased risk for ROP as they increase retinal oxygen levels by an increase in oxygen carrying capacity and a decrease in oxygen affinity of the red blood cell, caused by transfusing infants with adult hemoglobin having a reduced oxygen affinity as compared to fetal hemoglobin. A second explanation may be that blood transfusions increase the free, non-protein bound iron load leading to the production of free oxygen radicals that can cause irreversible damage to the developing retinal vessels.[5]

Last, an unintended side effect of RBC transfusions could be the concomitant administration of high doses of IGF-1. Hübler et al[6] reported that the IGF-1 load in RBC transfusions is equivalent to a single dose of 1 µg/kg, which is 5-10% of the adult dose. Hellström et al showed that a rapid increase in IGF-1 together with high levels of VEGF induces rapid growth of new vessels.[2] Based on this model, we hypothesize that artificial administration of IGF-1 via RBC transfusions causes a misbalance in IGF-1 and VEGF levels, resulting

Table 1 Characteristics of the twins

	Twin 1		Twin 2	
	Donor	**Recipient**	**Donor**	**Recipient**
Birth weight (g)	771	900	1270	1590
Gestational age (wks)	28+1	28+1	31+1	31+1
Prenatal glucocorticoïds	Yes	yes	Yes	yes
AV (days)	8	0	7	0
RDS (grade 2-3)	Yes	no	No	no
Inhaled NO	Yes	no	No	no
Transfusions	9	0	12	0
ROP				
ROP stage	5	no ROP	3	no ROP
Plus disease	Yes	no	Yes	no
First screening	33+4	33+4	37+4	37+4
PMA ROP	35+3		37+4	
PMA severe ROP	41+5		37+4	
ROP treatment	Laser Vitrectomy Lensectomy		Laser Vitrectomy Lensectomy	

in instant growth of neovascularizations in case of concomitant high levels of VEGF or postponement of neovascular growth when VEGF levels are low.

With this letter we want to create more awareness for those infants delivered after TTTS who need high numbers of RBC transfusions. Although their peripheral retina may be largely vascularized, they can develop potentially blinding ROP in a rapid and progressive way and should therefore be monitored closely so treatment can be in time and blindness can be prevented.

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