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Effect of Early Aggressive Intravenous Fat Emulsion Introduction on the Incidence of Retinopathy of Prematurity

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Abstract

Background: This study aimed to evaluate the effect of early aggressive introduction of intravenous fat emulsion (IVFE) on the occurrence of retinopathy of prematurity (ROP).

Patient and Methods: A retrospective study conducted at Prince Hashem Ben Al- Hussein Military Hospital between 2016-2017. A 100 premature infants of ≤ 34 weeks gestational age (G.A) and / or of <1500 grams, all who needed oxygen support for respiratory distress syndrome and who not received and who received either early aggressive or late non- aggressive intravenous fat emulsion and all who underwent an eye examination for retinopathy of prematurity.

Results: Of the total 100 (49 Males: 51 Females) premature infants studied 17 (17%) found to have ROP of them (7 males and 10 females) and 11 (64.7%) found to have unilateral involvement and 6 (35.3%) had bilateral involvement. Stage 3 and more found to associate with bilateral eye disease in 80% of patients. Seven percent have had stage (1), 5% stage (2), 4% stage (3), 1% stage (4) and none had stage (5). Of the 32 premature infants who received early aggressive IVFE (15 Males and 17 Females) 4 (12.5%) diagnosed to have ROP of them (2 males and 2 females), with 3 unilateral ROP and 1 with bilateral ROP. 9.4% with stage (1), 3.1% with stage (3) and none of them had stage 2,4 or 5. Of the 33 preterm infants who received late non aggressive IVFE (16 Males and 17 Females) 5 (15%) documented to have ROP, of them (2 males and 3 females). Unilateral involvement found in 4 (80%) where bilateral involvement in 1 (20%) of them. In this group 6% had stage (1), 2% stage (2), 3% stage (3) and no single preterm infant had stage 4 or 5. Of the 35 premature infants who did not receive IVFE at all (18 Males and 17 females) 8 (22.8%) developed ROP of them 3 males and 5 females. Four (50%) had unilateral ROP and 4 (50%) had bilateral diseased eyes. 5.7% developed stage (1) ROP, 8.5% stage (2), 5.7% stage (3), 2.8% stage (4) and none had stage 5. Premature infants ≤ 1200 grams or/ and ≤ 32 weeks of gestation at birth have had the highest incidence (35.9% and 25.5% respectively) and more severe form of the disease. The occurrence of retinopathy of prematurity is more common in females than males (M:F=14.3%:19.6%) and unilateral involvement much more than bilateral involvement (64.7%:35.3%).

Conclusion: Early aggressive introduction of intravenous fat emulsion associated with better retinal development in preterm infants and thus decrease the incidence of retinopathy of prematurity.

Keywords: Premature infant, Fat emulsion, Retinopathy of prematurity

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Introduction

Retinopathy of prematurity (ROP) or retrolental fibroplasia is a postnatal proliferative disorder of the immature retinal vasculature of the eyes of prematurely born infants in which the retinal blood vessels branch excessively and so increase in number [1,2]. Of all prematurely born infants 16% develop ROP and this rising up to 65% of infants weighing less than 1,250 kg at birth [1,2].

Poor vision and permanent blindness are the expected outcomes of preterm infants who progress to a severe form of ROP. DHA is found in high concentrations in the photoreceptors of the retina and supplies lipids to the retinal membrane. In the outer segments of the retina more than 50% of the fatty acid content is DHA.

This high concentration most likely due to permeability and fluidity of DHA's [2].

Moreover, DHA plays a vital function in developing vision acuity. It has been noted that an

Table 1: ROP distribution regarding gestational age.

TPN		Early aggressive TPN Of (32) pts (12.5%) affected						Late non-aggressive TPN Of (33) pts (15%) affected						NO TPN Of (35) pts (22.8%) affected					
Stage of ROP		NL	1	2	3	4	5	NL	1	2	3	4	5	NL	1	2	3	4	5
GA (wk)	Gender																		
28-29	M	1						2		1				2		1	1		
	F	2			1			2			1			1			1	1	
30-31	M	4	2					6		1				6	1				
	F	5						4	1					3		1			
32-33	M	5						4						6		1			
	F	5	1					4	1					4					
33-34	M	3						2						2					
	F	3						4						3	1				

Table 2: ROP distribution regarding birth weight.

TPN		Early aggressive TPN(32) pts						Late non-aggressive TPN(33) pts						NO TPN (35) pts					
Stage of ROP		N	1	2	3	4	5	N	1	2	3	4	5	N	1	2	3	4	5
Bwt(gm)	gender																		
800-900	M	0						0						1					
	F	0			1			0			1			0				1	
901-1000	M	1						1						1					
	F	1						1		2				0		1	1		
1001-1100	M	2						2						2					
	F	1						2	2					1		1	1		
1101-1200	M	1						1						1	1	1			
	F	1	1					2						3					
1201-1300	M							3						2					
	F	32	2					2						3	1				
1301-1400	M	3						3						4					
	F	3						2						2					
1401-1500	M	3						4						5					
	F	7						5						2					

abnormal visual functioning occurs when levels of DHA are too low [3]. During the third trimester, there is a massive transfer of the long chain polyunsaturated fatty acids (LCPUFAs) omega-3 and omega-6 from the mother to the fetus which probably prevents the development of retinopathy in full term babies, in part, this might occur because these mediators suppress the inflammatory protein that called tumor necrosis factor alpha (TNF-alpha), which is found in one type of cell, called microglia, which is closely associated with retinal blood vessels [4]. We hypothesize that preterm labor causes the lack of these essential nutrients which might contribute to ROP development in preterm infants. The aim of this study is to evaluate the effect of early aggressive IVFE introduction to premature infants on the occurrence of ROP.

Patients and Methods

A retrospective study conducted at Prince Hashem Ben Al-Hussein Military Hospital between 2016-2017. A total of 100 premature infants (49 males and 51 females) of ≤ 34 weeks gestational age and /or of < 1500 grams, all who needed oxygen support for respiratory distress syndrome were divided into three groups; 1- Who did not receive any kind of IVFE, 2- Who received early aggressive intravenous fat emulsion (2 grams of 20% Intralipids/kg/day since the first day of life) and advanced by 1 gram/kg/day till 3.5grams/kg/day, and 3- Who received late IVFE starting from day three of life at 1 gram/kg/day and advanced by one gram/kg/day till 3.5 grams/kg/day. All who underwent an eye examination for retinopathy of prematurity by the pediatric ophthalmologist who was not aware of the aim of the study.

Data collected from the records at pediatric ophthalmologist clinic first then from the medical files of premature infants in the NICU and then after that systematically analyzed. The same method and protocol of eye examination conducted by the same pediatric ophthalmologist for all premature infants. Severity of ROP classified as follows:

- Stage I: There is mildly abnormal blood vessel growth.
- Stage II: Blood vessel growth is moderately abnormal.
- Stage III: Blood vessel growth is severely abnormal.
- Stage IV: Blood vessel growth is severely abnormal and there is a partially detached retina.
- Stage V: There is a total retinal detachment.

Ethical approval was taken from JRMS ethical committee.

Results

Analyzing data shown in Table 1, 2, 3,4 and 5. We can read the following results: Of total 100 (49 Males: 51 Females) premature infants studied 17 (17%) found to have ROP of them (7 males and 10 females) and 11 (64.7%) found to have unilateral involvement and 6 (35.3%) had bilateral involvement. Stage 3 and more found to associate with bilateral eye disease in 80% of patients. 7% have had stage (1), 5% stage (2), 4% stage (3), 1% stage (4) and none had stage (5).

Of the 32 premature infants who received early aggressive IVFE (15 Males and 17 Females) 4 (12.5%) diagnosed to have ROP of them (2 males and 2 females), with 3 unilateral ROP and 1 with bilateral ROP. 9.4 % with stage (1), 3.1% with stage(3) and none of them had stage 2,4 or 5.

Of the 33 preterm infants who received late non aggressive IVFE (16 Males and17 Females) 5 (15%) documented to have ROP, of them (2 males and 3 females). Unilateral involvement found in 4 (80%) where bilateral involvement in 1 (20%) of them. In this group 6% had stage (1), 2% stage (2), 3% stage (3) and no single preterm infant had stage 4 or 5 Of the 35 premature infants who did not receive IVFE at all (18 Males and 17 females) 8 (22.8%) developed ROP of them 3 males and 5 females. Four (50%) had unilateral ROP and 4 (50%) had bilateral diseased eyes. 5.7% developed stage (1) ROP, 8.5% stage (2),

Table 3: Stages of ROP.

STAGES OF ROP	TOTAL SAMPLE of 100 pts (17%)affected	Early aggressive TPN of 32 pts (12.5%) affected	Late non-aggressive TPN of 33 pts (15%)affected	NO TPN of 35 pts (22.8%) affected
Stage 1 **Unilateral** **bilateral**	7 (7%) 6(83.3%) 1(16.6%)	3 (9.4%) 2(75%) 1(25%)	2 (6%) 2(100%) 0	2 (5.7%) 2(100%) 0
Stage 2 **Unilateral** **bilateral**	5 (5%) 4(80%) 1(20%)	0	2 (6%) 2(100%) 0	3 (8.5%) 2(66.6%) 1(33.3%)
Stage 3 **Unilateral** **Bilateral**	4 (4%) 1(25%) 3(75%)	1 (3.1%) 1(10%)	1 (3%) 0 1(100%)	2 (5.7%) 0 2(100%)
Stage 4 **Unilateral** **bilateral**	1 (1%) 0 1(100%)	0	0	1 (2.8%) 0 1(100%)
Stage 5 **Unilateral** **bilateral**	0	0	0	0

Table 4: ROP prevalence among preterm infants with different gestational ages.

	Total sample	Early aggressive TPN	Late non-aggressive TPN	NO TPN
28-29	7 (41.2%)	1 (25%)	2 (33%)	4 (57%)
30-31	6 (17.6%)	2 (18.2%)	2 (16%)	2 (18%)
32-33	3 (9.6%)	1 (9%)	1 (11%)	1 (9%)
33-34	1 (5.8%)	0	0	1 (16.6%)

Table 5: ROP prevalence among preterm infants with different birth weight.

Birth weight(gm)	Total sample	Early aggressive TPN	Late non-aggressive TPN	NO TPN
800-900	3(100%)	1(100%)	1(100%)	1(100%)
901-1000	4(44.4%)	0	2(50%)	2(60%)
1001-1100	4(33%)	0	2(50%)	2(40%)
1101-1200	3(25%)	1(33%)	0	2(33%)
1201-1300	3(16.6%)	2(28.5%)	0	1(16%)
1301-1400	0	0	0	0
1401-1500	0	0	0	0

5.7% stage (3), 2.8% stage (4) and none had stage 5.

In all 3 groups, premature infants ≤ 1200 grams or/ and ≤ 32 weeks of gestation at birth have had the highest incidence (35.9% and 25.5% respectively) and more severe form of the disease.

Even it is uncommon to have retinopathy of prematurity after the 33-34 week of gestation at birth in our study one female preterm borne at 34 weeks of gestation and who not received IVFE at all, found to have stage (1) bilateral ROP.

In general we found that in all groups the occurrence of retinopathy of prematurity is more common in females than males (M:F=14.3%:19.6%) and unilateral involvement much more common than bilateral involvement (64.7%: 35.3%).

Discussion

Lipid emulsions are composed of three elements: triglycerides, phospholipids and glycerol. Fatty acids are categorized into saturated, monounsaturated, and polyunsaturated fatty acids (LCPUFAs). Linoleic acid (C 18:2ω-6) and α -linolenic acid (C 18:3ω-3) are considered essential fatty acids. In the liver both Linoleic and alpha-linolenic acid underwent further metabolization to more unsaturated and longer-chain ω-6 and ω-3 fatty acids . The most important metabolite of linoleic acid is Arachidonic acid [AA] (C 20:4ω-6). Eicosapentaenoic acid [EPA] (20:5ω-3) and Docosahexaenoic acid [DHA] (22:6ω-3) are formed from linolenic acid [5-7].

Studies in a mouse model found that mice fed on the omega-3 diet had less initial vessel loss and had nearly 50% less pathological vessel growth than those fed on omega-6 diet [8]. Production of tumor necrosis factor-alpha (TNF-a), a key inflammatory mediator found to be decreased in the retinas of mice on the omega - 3 diet and increased in the retinas of mice on omega - 6 diet. Thus inflammation was also implicated in the pathogenesis of ROP.

In an attempt to improve growth, during the first week of life in preterm infants a newly published studies [5,9] has shown that an increase in intake of intravenous fat emulsions (omega 6), where is no omega-3 PUFA was given, was well tolerated with no significant adverse effects.

Lisa G Smithers et al. [10] showed that Higher dose of docosahexaenoic acid in the neonatal period improves visual acuity of preterm infants. John Paul San Giovanni et al. [11] showed that preterm infants fed high DHA formula have better visual resolution acuity than non-DHA supplemented formula fed premature formula.

In a study performed at the University of Chicago Medical Centre on preterm infants with birth weight < 1750 g with respiratory distress syndrome, who had not received any nutrition by day three of life and who were expected to receive parenteral nutrition for at least five subsequent days Hammerman et al. [12] reported an increase in

the incidence of ROP in the early lipid group to no early lipid group.

A study performed by Gilbertson et al. [13] at Charing Cross and Westminster Medical school, London on preterm infants < 1500 g birth weight, age <6 hrs, ventilator dependence, requirement for intensive medical and nursing care and estimated need for total parenteral nutrition for at least one week, also a study by Sosenko et al. [14] performed in the University of Miami School of Medicine, USA on preterm infants 600 g to 1000 g, requirement of mechanical ventilation at six postnatal hours for the 600 g to 800 g infants, and requirement for mechanical ventilation plus supplemental oxygen at six postnatal hours for the 800 g to 1000 g infants and a study by Ibrahim et al. [15] performed at Louisiana State University Health Sciences Center-Shreveport, USA on 32 ventilator-dependent preterm infants 501 to 1250 g. The Early Total Parenteral Nutrition (ETPN) group received 3.5 g/kg/day amino acids (AA), and 3 g/kg/day of 20% Intralipid (IL), starting within 1 hour after birth. The Late Total Parenteral Nutrition group (LTPN), started on a solution containing glucose during the first 48 hours of life, followed by 2 g/kg/day of AA and 0.5 g/kg/day of IL. For the LTPN group AA and IL were each increased by 0.5 g/kg/day to a maximum of 3.5 and 3 g/kg/day, respectively. All the above 3 mentioned studies have not found any significant difference in the incidence of ROP between early and no early lipid groups.

In their study on 100 preterm infants between 750 g and 1500 g, at Neonatal Intensive Care Unit, Children's Hospital of Illinois. Where the control group began treatment with 0.5 g/kg per day of 20% IVFE on the first day of TPN, and the experimental group began treatment with 2 g/kg per day of 20% IVFE on the first day of TPN. Drenckpohl et al. [9] showed that there was a significant increase in the incidence of ROP in no early lipid group, compared with the early lipid group.

Evaluate the effect of IVFE on ROP was not the aim in all above mentioned studies, but as secondary outcomes. Our study is the first study aimed to evaluate the effect of early aggressive introduction of intravenous fat emulsion (IVFE) on the occurrence of retinopathy of prematurity (ROP).

Our data come to support the result of Drenckpohl et al. study and to show that 17% of premature infants who are born at ≤ 34 weeks of gestation and / or ≤ 1500 grams can develop retinopathy of prematurity. Females much more affected than males (19.6%:14.3%), and unilateral involvement much more common than bilateral involvement (64.7%: 35.3%). Premature infants ≤ 1200 grams or/ and ≤ 32 weeks of gestation at birth have the highest incidence (35.9% and 25.5 % respectively) and more severe form of the disease. Preterm infants who started on early aggressive IVFE had lower incidence of ROP than those who received late or no IVFE (12.5%, 15% and 22.8% respectively) and at the same time had a less severe form of the disease than preterm infants who did not receive IVFE at all.

Even it is uncommon to have retinopathy of prematurity after the 33 weeks to 34 weeks of gestation at birth in our study one female preterm borne at 34 weeks of gestation and who not received IVFE at all, found to have stage one bilateral ROP.

Due to small size included in our study further research on the effect of aggressive intravenous intralipid on ROP is recommended.

Conclusion

Early aggressive introduction of intravenous fat emulsion associated with better retinal development in preterm infants and thus decrease the incidence of retinopathy of prematurity.

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