ISSN: 0976-3031

International Journal of Recent Scientific Research

Impact factor: 5.114

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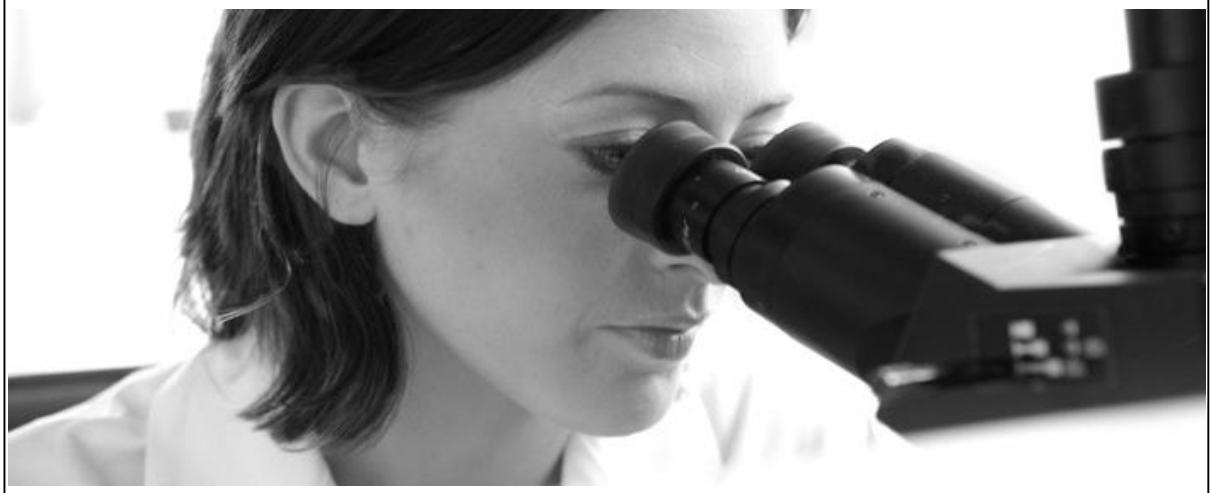

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Volume: 6 Issue: 9

THE PUBLICATION OF
INTERNATIONAL JOURNAL OF RECENT SCIENTIFIC RESEARCH
http://www.recentscientific.com
E-mail: recentscientific@gmail.com

ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 6, Issue, 9, pp.6466-6470, September, 2015

International Journal of Recent Scientific Research

RESEARCH ARTICLE

EVALUATION OF SERUM INSULIN LIKE GROWTH FACTOR (I) IN RETINOPATHY OF PREMATURITY

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ARTICLE INFO

Article History:

Received 16th June, 2015
Received in revised form 24th July, 2015
Accepted 23rd August, 2015
Published online 28st September, 2015

Key words:

LBW, low birth weight; GA, gestational age; IGF-I, insulin-like growth factor I; ROP, retinopathy of prematurity; CRP, C - reactive protein.

ABSTRACT

Insulin-like growth factor I (IGF-I) had been shown to play a role in the patho-physiology of Retinopathy of prematurity (ROP) which may develop during the early weeks after preterm birth. A deficit of IGF-I in the first few weeks of post-natal life is a possible diagnostic marker for Retinopathy of prematurity.
Methods: Measuring serum IGF-I at 1st and 30th day of 74 infant with Gestational age (mean) 31.76±2.22 weeks (preterm cases group) and 20 full term infant with Gestational age (mean) 38.05±1.15 weeks (control group). All infants had Ophthalmic Fundus examination at 30th day of life.
Results: Five babies had developed ROP, their gestational age (mean) 29.6±0.89 weeks. Sixty nine babies had gestational age (mean) 31.91±2.21weeks had not develope ROP. Mean serum IGF-I level in preterm group was statistically significantly lower than that of control group .We found that the cut off points of IGF-1 between the ROP and non-ROP neonates preterm group are 27ng/ml. A significant association was found between the development of retinopathy and other variables as early gestational age, low birth weight, prolonged mechanical ventilation, sepsis and low levels of serum IGF-I in the fourth week.
Conclusions: These results indicate that persistent low serum concentrations of IGF-I after premature birth are associated with later development of ROP and other complications of prematurity.

INTRODUCTION

Preterm birth is defined as all births before 37 completed weeks of gestation or fewer than 259 days since the first day of a woman's last menstrual period. Preterm birth can be further subdivided based on gestational age as extremely preterm (< 28 weeks), very preterm (28 - < 32 weeks) and moderate preterm (32 - < 37 completed weeks of gestation) [1].Preterm birth is a common early life event, the adverse consequences of which can affect the entire life course. Worldwide, over 11% of babies are born preterm, a number that continues to rise in most regions[2].Retinopathy of prematurity (ROP) is the most widely recognized cause of visual impairment after preterm birth and is defined as a vision-threatening disease associated with abnormal retinal vascular development at the boundary of vascularized and avascular peripheral retina [3].

Oxygen plays a critical role in this process, with both hypoxia and hyperoxia affecting levels of growth factors, such as vascular endothelial growth factor, essential for normal retinal vascular development[4].Insulin like growth factor I (IGF-I) is a hormone similar in molecular structure to insulin. It plays an important role in childhood growth and continues to have anabolic effects in adults [5], (IGF-I) is a polypeptide hormone produced mainly by the liver in response to the endocrine GH stimulus, but it is also secreted by multiple tissues for autocrine / paracrine purposes. IGF-I is partly responsible for systemic GH activities although it possesses a wide number of own properties (anabolic, antioxidant, anti-inflammatory and cytoprotective actions [6]. Retinopathy of prematurity (ROP) is a blinding disease that may develop during the early weeks after preterm birth and characterised by an arrest in normal retinal vascular development. The disease is initiated by a decrease in vascular growth. The severity of neovascularisation and the stage of ROP are dependent on the amount of avascular retinal tissue present in the infant [7].

MATERIALS AND METHODS

This study was enrolled 94 neonate after obtaining written informed consent from their parents and approval of Ethics Committee of Menoufia University. Throughout the period of study from December 2013 to December 2014 at Menoufia University Hospital NICU They were divided into two groups; Group I (cases group): 74 preterm neonate with Gestational age mean 31.76±2.22 weeks .Group II (control group): 20 full term

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neonate with Gestational age mean 38.05±1.15 weeks. Premature neonates were subdivided to Group (Ia) were had retinopathy of prematurity. Group (Ib) were had not retinopathy of prematurity. Inclusion criteria (cases group) included in the study had gestational age between (28 to 36 weeks) and had considered at risk for ROP by standard criteria e.g. oxygen therapy, apnea, anemia, sepsis and low birth weight. And 20 neonates (Control group) were full term neonates (more than 37 week) without risk for ROP by standard criteria. Exclusion criteria were Neonates with obvious congenital malformations and with other causes for retinopathy also inability to complete postnatal clinical follow-up until an age corresponding to 40 postmenstrual weeks.

On admission, every patient was meticulously examined as follows:-Detailed history taking, full clinical examination, Routine investigations .Specific investigations; which is **(**IGF-I) analysis. Serum Venous blood samples (0.5 mL) will be taken at (1st day and 30th day) for cases group and at (1^{st} day) for control group .either during stay in neonatal intensive care unit or after discharge and stored at -80°C. All samples from an individual infant were analyzed in the same assay. Separate serum by centrifugation at room temperature followed by assay by ELISA. Fund us examination had performed by the ophthalmologist to detect ROP at 4^{th} week postnatal age by indirect ophthalmoscope.

Statistical analysis

The data were collected, tabulated, and analyzed by SPSS (statistical package for social science) version 17.0 on IBM compatible computer (SPSS Inc., Chicago, IL, USA). Two types of statistics were done. Descriptive statistics e.g. percentage (%), mean (x) and standard deviation (SD) and Analytic statistics which include the following tests as analysis of variance (F), with a level of significance as follows : p value less than 0.05 was considered significant, p value less than 0.001 as highly significant, and greater than 0.05 as non significant. Also we used Fisher's exact test, Z test, T-test, Mann Whitney U test, Paired t-test, Analysis of variance (ANOVA), Spearman correlation (r), Odds ratio (OR), Regression analysis, Receiver operating characteristic (ROC), or simply ROC curve.

RESULTS

Regarding the demographic data. There is significance difference between group (Ia) and group (Ib) cases regarding the gestational age (P<0.05) while non significance difference between group (Ia) and group (Ib) regarding the sex, twins pregnancy, consanguinity, maternal disease and type of delivery were found. There are 5 cases with ROP from 74 preterm neonate examined .The percentage of cases with ROP 6.75% as in (Table 1). Also regards interventions done there is significance difference between group (Ia) and group (Ib) regarding the use of CPAP (P<0.05) as in (Table 2) while no significance difference between group (Ia) and group (Ib) regarding use of mechanical ventilation, nasal O2 and blood transfusion. Regards the clinical data it Shows that there was significance difference between group (Ia) and group (Ib) regarding the weight, heart rate, respiratory rate and sepsis (P<0.05) as in (Table 3) while non-significance difference regarding the temperature, neonatal reflexes, presence of convulsions or jaundice were found. (Table 4) it Shows that there was significance correlation between IGF-1 and Gestational age , Weight , CRP , Period of CRP positivity and Duration of mechanical ventilation between cases with retinopathy of prematurity (Ia) and without (Ib) regarding the level of IGF-I at 1^{st} and 30^{th} day (P< 0.05) . (Table 5) Shows that there is significance difference between cases with retinopathy of prematurity and without, regarding the level of IGF I at 30th day, (P< 0.05) and non significance difference at 1st day.

Table 1 Comparison between cases with ROP and without as regards demographic data

	ROP					
	Group Ia N = 5		**Group Ib N = 69**		**Test of significance**	**P value**
Gestational age (Weeks) X ±SD	29.6±0.89		31.91±2.21		Mann Whitney 2.27	0.02 S *
Range	28 – 30		28 – 35			
	No	%	No	%	Fisher's Exact test	
Sex						
Male	48	69.6	2	40	1.86	0.32
Female	21	30.4	3	60		
Twines						
Yes	2	40	6	8.7	4.74	0.09
No	3	60	63	91.3		
Consanguinity						
Yes	2	40	18	26.1	0.46	0.61
No	3	60	51	73.9		
Mother disease						
Yes	0	0	18	26.1	1.72	0.33
No	5	100	51	73.9		
Type of delivery						
NVD	1	20	19	27.5	0.13	1.0
CS	4	80	50	72.5		

Table 1 Shows that there was significance difference between group I a and group I b regarding the gestational age (P<0.05) while non significance difference between group I a and group I b regarding the sex, twins pregnancy, consanguinity, maternal disease and type of delivery were found. There are 5 cases with ROP from 74 preterm neonate examined .The percentage of cases with ROP 6.75%.

Table 2 Comparison between cases with ROP and without as regards interventions done for the studied groups

	ROP				**Fisher's Exact**	**P value**
	Group Ia N = 5		**Group Ib N = 69**			
	No	**%**	**No**	**%**		
Mechanical ventilation						
Yes	2	40.0	42	60.9	0.84	0.39
No	3	60.0	27	39.1		
CPAP						
Yes	5	100	29	42.0	6.31	0.02*
No	0	0.0	40	58.0		
Blood transfusion						
Yes	2	40.0	30	43.5	0.02	1.0
No	3	60.0	39	56.5		
Nasal O2						
Yes	5	100	63	91.3	0.47	1.0
No	0	0	6	8.7		

Table 2 Shows that there was significance difference between group I a and group I b regarding the use of CPAP (P<0.05) while no significance difference between group I a and group I

b regarding use of mechanical ventilation, nasal O2 and blood transfusion.

Table 3 Comparison between cases with ROP (Ia) and without (Ib) as regards clinical data

	ROP				Mann Whitney	P value
	Group Ia N = 5		Group Ib N = 69			
Weight						
X ±SD	1.03±0.06		1.55±0.41		3.15	0.002*
Range	0.96 – 1.1		0.75 – 2.65			
Temperature						
X ±SD	36.2±0.27		36.26±0.76		0.11	0.91
Range	36 – 36.5		35 – 37.5			
Heart rate						
X ±SD	168.0±10.95		148.43±18.06		2.10	0.036*
Range	160 – 180		120 – 180			
Respiratory rate						
X ±SD	90.4±8.76		76.87±15.63		1.97	0.049*
Range	84 – 100		50- 120			
	No	%	No	%	Fisher's Exact	
Neonatal reflexes						
Good	0	0	20	29.0	1.99	0.32
Weak	5	100	49	71.0		
Convulsions						
Yes	0	0	22	31.9	2.27	0.31
No	5	100	47	68.1		
Jaundice						
Yes	5	100	49	71.0	1.99	0.32
No	0	0	20	29.0		
Sepsis						
Yes	5	100	41	59.4	3.26	0.05 *
No	0	0	28	40.4		

Table 3 Regards the clinical data it Shows that there was significance difference between group I a and group I b regarding the weight, heart rate, respiratory rate and sepsis (P<0.05) while non-significance difference between group I a and group I b regarding the temperature, neonatal reflexes, presence of convulsions or jaundice were found.

Table 4 Spearman correlation between IGF1 and other parameters for cases group (I a) and group (I b)

	IGF1(1st day)		IGF1(30th day)	
	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value
Gestational age/ week	+ 0.63	<0.001*	+ 0.55	<0.001*
Weight	+ 0.59	<0.001*	+ 0.59	<0.001*
Temperature	+ 0.18	0.08	+ 0.31	0.02*
Heart rate	- 0.27	0.009	- 0.08	0.52
Respiratory	- 0.65	<0.001	- 0.22	0.10
Hb	+ 0.23	0.06	+ 0.04	0.78
WBCs	- 0.05	0.68	- 0.39	0.03
Platelets	+ 0.13	0.32	+ 0.09	0.53
CRP	- 0.54	<0.001*	- 0.70	<0.001*
Period of CRP positivity	- 0.42	0.07	- 0.72	<0.001*
Duration of mechanical ventilation	- 0.35	0.02*	- 0.60	<0.001*
Duration of CPAP	- 0.14	0.45	- 0.13	0.52
Duration of Nasal O2	+ 0.16	0.20	+ 0.23	0.08

Table 4 Shows that there was significance correlation between IGF1 and Gestational age ,Weight , CRP , Period of CRP positivity and Duration of mechanical ventilation between cases with retinopathy of prematurity (Ia) and without (Ib), regarding the level of IGF I at 1st and 30th day (P< 0.05) .

Table 5 Comparison between cases with retinopathy of prematurity and without as regards serum level of IGF-I

	Retinopathy of prematurity		Mann Whitney	P value
	Group Ia N = 5	Group Ib N = 69		
IGF1 (1st day)				
X ±SD	16.0±9.0	26.06±11.68	1.77	0.08
Range	7 – 28	4 – 50		NS
IGF1 (30th day)		N = 55		
X ±SD	29.6±18.02	46.54±16.66	1.99	0.047
Range	16 – 60	20 – 88		S *

Table 5 Shows that there was significance difference between cases with retinopathy of prematurity and without, regarding the level of IGF I at 30th day, (P< 0.05) and non significance difference at 1st day.

DISCUSSION

Retinopathy of prematurity (ROP) is the major cause of blindness, and it is a main cause of blindness worldwide. ROP-induced vision impairment or blindness significantly impairs the quality of life of preterm infants [8]. Retinopathy of prematurity is starting with impaired retinal vessel growth in the neonatal period. Weeks to months later, peripheral retinal hypoxia induces pathologic neo-vascularization that may lead to retinal detachment and blindness [9].The importance of nutrition and factors such as insulin-like growth factor-1 and omega -3 long chain fatty acids for proper retinal vascularization has been defined [9]. Insulin like growth factor I (IGF-1) which is nutrition dependent, is essential for brain, muscle, bone and vascular growth and remodeling pre- and postnatally it mediated mainly through the IGF-1 receptor (IGF-1R) and regulated by at least six IGF-binding proteins (BPs). IGFBP-1 and IGFBP-3 appear to be the most important for fetal growth regulation [9]. In our study the prevalence of ROP was 6.75%, while in another study in Egypt the prevalence of ROP was 19.2% [10].This may be due to small number of cases and gestational age < 36 weeks and wide range of birth weight.

The prevalence of ROP was 12.8% in a larger study in china [11]. In our study there was no statistically significant difference in the incidence of ROP between males and females (p = 0.32) so the gender was not a significant factor. In accordance with (Friling *et al*., 2007)[12].Regarding the effect of birth weight (BW) on the occurrence of ROP, we found that it was a highly significant risk factor (p<0.001). This is in agreement with (Perez *et al*., 2010) [13] who stated that lower birth weight in preterm infants was significantly associated with development of ROP. This may be due to more susceptibility for oxygen therapy, sepsis in VLBW infants [13]. Regarding CRP level, our results showed high significant difference between the studied group (Ia) and group (Ib) (P < 0.001) regarding CRP being higher in group (Ia) .with ROP than group (Ib) without ROP. In accordance with (Pérez *et al*., 2014) [14], who found there was a significant association was found between the development of retinopathy and sepsis during the first three weeks. Also (Turner *et al*., 2006) [15] have analyzed and found to be strongly correlated with the development of ROP. Regarding interventions done, like mechanical ventilation and CPAP and blood transfusion our

results showed high significance difference between group (Ia) more than group (Ib) (P<0.001) This was confirmed by (Krishna *et al*., 2006) [16], who stated that oxygen therapy is a significant risk factor in developing ROP. They reported that oxygen toxicity is induced directly by highly reactive oxygen free radicals and strong factor induce (ROP). Also in accordance with (Valieva *et al*., 2009) [17] that found that blood transfusions were more common in NICUs and some researchers considered them as a risk factor for developing ROP. Regarding the present work analysis of the cytokines of group I (cases) and group II (controls) revealed that the mean serum IGF-I level in group I was statistically significantly lower than that of control group (p<0.001), and in group (Ia) less than group (Ib) that make IGF-I has a critical role in normal development of retinal vessels, and its lack may be associated with impaired normal vascular growth and subsequent proliferative ROP. Our results are in agreement with (Perez *et al*., 2010) [13], who found that the mean IGF-1 in ROP group was statistically significantly lower than that of control group. IGF-1 is considered a protecting factor against ROP [13]. There are indeed, premature babies with normal post-natal weight gain but low levels of IGF-1 who develop ROP. On the other hand, many children have poor weight gain, high IGF-1 level and do not develop ROP [14]. Agreement with (Hellstrom *et al*., 2010) [18], who found that low serum levels of IGF-I and poor early weight gain during the first months of life have been found to be correlated with severity of ROP [18]. We found that the cut off points of IGF-1 and between the ROP and non-ROP neonates are 27 ng/ml. This agreed with (Villegas *et al*., 2006), who found the cut off points of IGF-1 and between the healthy and non-healthy neonates are 22 ng/ml [19], respectively. IGF-1 has 91.2% sensitivity in the diagnosis of ROP. Accordingly, IGF-I can serve as high sensitivity indicators in ROP screening. Studying IGF-I levels, they give a better indication of the status of the newborn, in terms not only of nutrition, since good nutritional status and postnatal growth are associated with increases in IGF-I, but also several other factors such as the development of sepsis, bronchopulmonary dysplasia and all of which are associated with diminished levels of IGF-I [20].Other parameter that we have analyzed and found to be strongly correlated with the development of ROP is the presence of sepsis in the first three weeks post-partum, as defined by clinical, analytical or microbiological criteria[15].The importance of sepsis has previously been described, while the current study shows that its combination with IGF-I levels increases the accuracy of prediction of ROP.

CONCLUSIONS

Several risk factors were found to be associated with the development of ROP in preterm infants. The percentage of ROP 6.75% for the examined preterm cases. Low IGF-I (< 27 ng/ml) serum level can be useful as indicators in ROP screening and determination of IGF-I level in the 4th week post-partum provides a sufficient and reliable prognostic tool and allows the identification of a group of neonates at high risk of developing ROP and we suggest that LBW, small GA, oxygen therapy, long duration of incubation, CPAP, neonatal sepsis and critical illness of the neonate were the major risk factors for ROP.

Acknowledgments

I would like to express my sincere thanks to Prof. Fady Mohamed El Gendy , Prof. Khalid Abdul Momin Ali, Dr. Dina Abdel Razik Midan, Dr. Moataz Fayez El Sawy for kind supervision and guidance were indispensable all through the work. And my special thanks to my patients and their families for their cooperation without which this work had done.

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How to cite this article:

Mohamed Kamal Elsayed Mahmoud *et al*.2015, Evaluation of Serum Insulin Like Growth Factor (I) in Retinopathy of Prematurity. *Int J Recent Sci Res*, 6(9), 6466-6470.

International Journal of Recent Scientific Research

ISSN 0976-3031