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Effect of Vitamin (A) and Beta-Blockers Supplementation on Retinopathy of Prematurity Among Preterm Newborns

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ABSTRACT

Background: Retinopathy of prematurity (ROP), a condition that has been well-known for more than 50 years in nations with low perinatal death rates, has developed an epidemic pattern in recent years in a number of growing economies with advanced populations.

Objective: To study ROP among our preterm newborns and to assess the effect of vitamin A and beta-blockers supplementation on ROP if it exists.

Patients and Methods: The present study was carried out on 186 preterm newborns of both sexes who were admitted to NICU, Pediatric Department at Menoufia University Hospitals from October 2019 to March 2020.

Results: Advancement from grade I to grade II occurred significantly lesser among those who received vitamin A (4.55%) in comparison to beta blockers group (59.09%) and judicious O_2 group (36.36%) (P<0.001). Those who were free of ROP at 2 weeks and became grade I at 4 weeks, occurred significantly more among those on judicious O_2 (100%) in comparison to beta blockers group (0%) and vitamin A group (0%) (P=0.023). Also, among those who were grade I at 2 weeks and remained grade I with no progression at 4 weeks, occurred significantly more in vitamin A group (69.23%) in comparison to beta blockers group (7.69%) and judicious O_2 group (23.08%) (P<0.001).

Conclusion: Vitamin A and to a lesser extent beta blockers supplementation have an important role in decreasing the morbidity among the newborns. Early administration of vitamin A (1500 IU/day as early as possible) and beta blockers (0.5-2 mg/kg/day) in neonates may help decrease the progression of ROP grading.

Keywords: Vitamin (A), Beta Blockers Supplementation, Retinopathy of Prematurity, Preterm Newborns.

INTRODUCTION

Retinopathy of prematurity (ROP), a condition that has been well-known for more than 50 years in nations with low perinatal death rates, has recently been identified in numerous emerging-economy nations as having an epidemic trend [1]. Therefore, ROP is a danger for all preterm infants, and very low birthweight is an additional risk factor. The optimal oxygen level for preterm infants at various ages is still unknown, and both oxygen toxicity and relative hypoxia can contribute to the onset of ROP. There are now more accurate ways to measure oxygen. As a result, the issue has diminished in frequency, particularly in industrialised nations [2].

ROP can be moderate and resolve on its own, but in more severe cases, it can result in blindness, placing a social and financial strain on the society. Children with irreversibly damaged eyesight may also experience delays in their cognitive and psychomotor growth [3,4]. By more nearly simulating the intrauterine environment following preterm delivery, ROP can be prevented. Such precautions are expected to lessen issues other than ROP as well. In addition to supplying some exogenous cofactors (such as vitamin A and beta blockers), these approaches include limiting harmful postnatal impacts (such as oxygen excess) that may minimise any stage ROP in preterm newborns [5,6].

One of the most significant micronutrients impacting children's health is vitamin A. Within the first two days of life, giving vitamin A supplements to newborn babies reduced infant mortality by about 25%, with those with low birth weights benefiting the most. Large dosages of vitamin A have been administered to this group as a preventative measure for chronic pulmonary illness with no apparent side effects noted. Retinoic acid (RA), an active metabolite of vitamin A, is said to have extremely effective anti-angiogenic action by reducing the production of vascular endothelial growth factor (VEGF) [7].

In cells, vitamin A (retinol) is changed into retinoic acid. In all preterm newborns who require a fraction of inspired oxygen above 21% upon admission, it is administered IM or orally at a dosage of 1500 IU three times per week for the first 28 days of life [8].

Beta-blockers may slow the progression of ROP or even reverse existing ROP because they affect the vaso-proliferative retinal pathway. Oral propranolol is a well-established treatment for many other newborn illnesses, such as congenital thyrotoxicosis, and it is given prophylactically to newborns with paroxysmal supraventricular tachycardia and long QT syndrome over extended periods of time. There have been no side effects reported when administered within the reference dose (0.5 - 2 mg/kg/day) for a duration that may extend to 3 or 6 months in some cases. Therefore, it can be taken within the advised range for a few weeks before recording the outcomes [9]. The aim of this study was to study ROP among our preterm newborns and to assess the effect of vitamin A and beta-blockers supplementation on ROP if it exists.

PATIENTS AND METHODS

The present study was carried out on 186 preterm newborns of both sexes who were admitted to NICU, Pediatric Department at Menoufia University Hospitals

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fulfilling the inclusion and exclusion criteria in the period from October 2019 to March 2020.

Patients grouping:

After NICU admission and stabilization, the patients were randomly subdivided into 3 groups. **Group 1 (62 patients):** Patients had vitamin A supplementation in addition to oxygen therapy. The preterm infants were given a daily dose 1500 IU/day in a drop form added to their enteral feeds as soon as minimal feeding was introduced. The duration of vitamin A supplementation was till the age of 28 days. **Group 2 (62 patients):** In addition to oxygen therapy, patients had oral beta-blockers supplementation in 0.5-1 mg/kg/day in 3 divided doses as soon as minimal feeding was introduced. Serial dose reduction for 5 to 7 days with serial measurement of heart rate, blood pressure and symptoms were done till complete withdrawal was achieved. **Group 3 (62 patients):** Patients on judicious oxygen therapy including those on mechanical ventilation that keeps the oxygen saturation within the recommended range (90% to 95%) for preterm babies.

According to the fundus examination, each group was sub-grouped into: **Free:** Who were free of ROP at time of examination. **I:** Who were diagnosed as grade I ROP at time of examination. **II:** who were diagnosed as grade II ROP at time of examination. **III:** Who were diagnosed as grade III ROP at time of examination. **IV:** Who were diagnosed as grade IV ROP at time of examination. **V:** Who were diagnosed as grade V ROP at time of examination.

Inclusion criteria: Gestational age <37 weeks, both sexes, <72h of age and those who needed respiratory support at 24h of age either by noninvasive respiratory support or mechanical ventilation.

Exclusion criteria: Neonatal sepsis, inborn errors of metabolism, terminal illness as evidenced by pH<7.0 for >2h or persistent bradycardia (heart rate <100 bpm) associated with hypoxia for >2h and parental refusal to participate in the study.

All patients were subjected to the following:

Detailed history taking regarding: 1) Prenatal history: including number of previous pregnancies, mother illness and whether controlled or not, drug intake, history of previous abortions. 2) Natal history: including the mode of delivery, abnormal presentation, gestational age, maternal risk factors e.g., UTI and birth trauma with bruising and/or fractures. 3) Postnatal history: including APGAR score and if any special resuscitation steps were required. 4) Family history: Previous sibling with the same condition, consanguinity, metabolic disorders.

Thorough clinical examination: General examination: Anthropometric measurements as weight, length, head circumference and abdominal girth, complexion included jaundice or pallor, vital signs as heart rate, blood pressure, respiratory rate and temperature, **Systemic examination:** Chest, abdomen, cardiac and neurological.

Routine work up included complete blood count [10], C reactive protein performed through a kinetic method by CRP eurolyser [11], serum bilirubin (Total and direct): analyzed by Cobas 111 analyzer [12], Renal function tests (Urea and Creatinine) analyzed through the fixed rate technique by spectrophotometer 574nm [13]. Liver function tests (SGOT and SGPT) analyzed through kinetic method by spectrophotometer wl 540 nm [14], blood culture whenever needed [15], random blood glucose by finger-prick test using the digital glucose meter with disposable strips, and arterial Blood gases whenever needed analyzed by the ST-200 CC arterial blood gas analyzer [16].

Fundus examination: It was implemented twice by an expert ophthalmologist. At 2 weeks old age then at 28 days old age.

Echocardiography: whenever needed using a GE Vivid E9 echocardiography equipment for the newborns with any of the following criteria: O_2 saturation < 90 % by pulse oximeter, significant heart murmur, O_2 saturation < 95 % by pulse oximeter in a one hand and a leg in 3 successive readings with an hour interval.

Ethical consideration:

The study protocol was authorised by Menoufia University's Ethical Scientific Committee, and parents gave their informed agreement before enrolling their infants in the study. The worldwide medical association's code of ethics, the Declaration of Helsinki for Humans, was adhered to throughout the course of this study.

Statistical analysis

Package for Social Science (IBM SPSS) version 20 was used. The confidence interval was set to 95% and the margin of error accepted was set to 5%. Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). So, the p-value <0.05 was considered significant level.

RESULTS

Regarding the demographic data and the clinical findings, there were no statistically significant differences between the three studied groups **(Table 1).**

Table (1): Demographic data and clinical findings of the three studied groups

	Groups			Test of significance *p*-value
	Vitamin A (n=62)	**□ blocker (n=62)**	**Judicious O_2 (n=62)**	
Sex - Male (n=93) Female (n=93)	 30 (48.39%) 32 (51.61%)	 31 (50.00%) 31 (50.00%)	 32 (51.61%) 30 (48.39%)	$\chi^2_{(df=2)}$ = 0.129 *p*=0.938 NS
Mode of delivery - CS (n=60) - Vaginal (n=126)	 17 (27.42%) 45 (72.58%)	 18 (29.03%) 44 (70.97%)	 25 (40.32%) 37 (59.68%)	$\chi^2_{(df=2)}$ = 0.2805 *p*=0.246 NS
Gestational age (Weeks) Min. – Max. Mean ± S.D. 95% CI for mean	 29.00-36.00 32.58±2.04 32.0613-33.1000	 29.00-36.00 33.11±1.95 32.6174-33.6084	 27.00-36.00 32.31±2.38 31.7024-32.9106	$F_{(df=2)}$=2.292, *p*=0.104 NS
Consanguinity	20 (32.26%)	17 (27.42%)	16 (25.81%)	$\chi^2_{(df=2)}$ = 0.686 *p*=0.710 NS
Birth weight (kg) - Min. – Max. - Mean ± S.D. - 95% CI for mean	 1.13-2.70 1.95±0.56 1.8086-2.0949	 1.00-2.80 2.06±0.50 1.9344-2.1908	 1.00-2.90 2.02±0.55 1.8758-2.154	$\chi^2_{(df=2)}$ = 0.655 *p*=0.521 NS
Head circumference - Min.– Max. - Mean ± S.D. - 95% CI for mean	 30.00-35.00 32.52±1.57 32.1263–32.9220	 30.00-35.00 32.52±1.57 32.1263–32.9220	 29.00-36.00 32.69±1.62 32.2820–33.1051	$F_{(df=2)}$= 0.800 *p*= 0.451 NS
Cardiac anomalies (n=16) (8.00%)	5 (8.05%)	8 (12.90%)	3 (4.84%)	$\chi^2_{(df=2)}$ = 2.599 *p*=0.273 NS
Skeletal anomalies (n=16) (8.00%)	1 (1.61%)	0 (0.00%)	3 (4.84%)	$\chi^2_{(df=2)}$ = 3.577 *p*=0.334 NS

χ^2: Chi square test, F: One-way ANOVA test, CS: Cesarian section, CI: confidence interval, NS: Statistically non-significant

Regarding the maternal risk factors, there were no statistically significant differences between the three studied groups in terms of maternal age, maternal diabetes, hypertension and drugs. Also, among those with ROP in comparison to those without ROP, there were no statistically significant differences as regards the maternal risk factors **(Table 2)**.

Table (2): Maternal risk factors of the three studied groups

	Groups			Test of significance *p*-value
	Vitamin A (n=62)	**□ blocker (n=62)**	**Judicious O_2 (n=62)**	
Maternal age (years) - Min. – Max. - Mean ± S.D. - 95% CI for mean	 19.00-36.00 25.55±4.45 24.4186–26.6782	 19.00-31.00 25.00±4.01 23.9811–26.0189	 18.00-35.00 25.66±5.10 24.3656–26.9570	$F_{(df=2)}$=0.376, *p*=0.687 NS
Maternal Diabetes mellitus (n=38) (20.43%)	10 (16.13%)	16 (25.81%)	12 (19.35)	$\chi^2_{(df=2)}$ = 1.852 *p*=0.396 NS
Maternal Hypertension (n=38) (20.43%)	15 (24.19%)	9 (14.52%)	14 (22.58%)	$\chi^2_{(df=2)}$ = 2.050 *p*=0.359 NS
Drugs (n=41) (22.04%)	12 (19.35%)	18 (29.03%)	11 (17.74%)	$\chi^2_{(df=2)}$ = 2.691 *p*=0.260 NS
	Retinopathy Overall		Test of Significance *p* value	
	No (n=142) (76.34%)	**Yes (n=**44) (23.66%)		
Maternal age (years) Min-Max Mean ± S.D. 95% CI for mean	 18.00-36.00 25.47±4.40 24.74-26.20	 18.00-35.00 25.18±4.97 23.67-26.69	$t_{(df=184)}$=0.370 *p=0.*712 NS	
Maternal Diabetes mellitus (n=38)	25 (17.61%)	13 (29.55%)	$\chi^2_{(df=1)}$ = 2.946, *p=0.*086 NS	
Maternal hypertension (n=38)	29 (20.42%)	9 (20.45%)	$\chi^2_{(df=1)}$ 0.000, *p*=0.996 NS	
Drugs (n=41)	31.00 (21.83%)	10 (22.73%)	$\chi^2_{(df=1)}$ = 0.016 *p=0.*900 NS	

Regarding the neonatal risk factors, there were no statistically significant differences between the three studied groups. Comparing those with ROP to those without ROP regarding the neonatal risk factors, we observed that there was a statistically significant association between ROP and O_2 using by its non-invasive (free O_2) and invasive ways (mechanical ventilation). 86.36% of those with ROP needed mechanical ventilation, 0.00% needed free O_2 while there was no statistically significant association with CPAP. Also, blood transfusion showed a statistically significant association with ROP. 34.09% of those with ROP needed blood transfusion **(Table 3)**.

Table (3): Neonatal risk factors of the three studied groups

	Groups			**Test of significance *p*-value**
	Vitamin A (n=62)	**□ blocker (n=62)**	**Judicious O_2 (n=62)**	
Free O_2 (n=68) (36.56%)	19 (30.65%)	30 (48.39%)	19 (30.65)	$\chi^2_{(df=2)}$ = 5.610 *p*=0.061 NS
CPAP (n=44) (23.66%)	12 (19.35%)	17 (27.42%)	15 (24.19%)	□*p*=0.568 NS
Mechanical ventilation (n=93) (50.00%)	31 (50.00%)	25 (40.32%)	37 (59.68%)	$\chi^2_{(df=2)}$ = 4.645 *p*=0.098 NS
Blood transfusion (n=27) (22.04%)	8 (12.90%)	9 (14.52%)	10 (16.13%)	$\chi^2_{(df=2)}$ = 0.260 *p*=0.878 NS
	Retinopathy Overall			
	No (n=142) (76.34%)	**Yes (n=**44) (23.66%)	Test of Significance *p* value	
Free O_2 (n=68)	59 (41.54%)	0 (0.00%)	$\chi^2_{(df=1)}$ = 18.749 ***p*<0.001*** Odds ratio (95%CI) 0.122 (0.041-0.359)	
CPAP (n=44)	37 (26.06%)	7 (15.91%)	$\chi^2_{(df=1)}$ = 1.915 *p=0*.166 NS	
Mechanical Ventilation (n=89)	46 (32.39%)	38 (86.36%)	$\chi^2_{(df=1)}$ = 39.506 ***p*<0.001*** Odds ratio (95%CI) 10.018 (3.973-25.261)	
Blood transfusion (n=27)	12 (8.45%)	15 (34.09%)	$\chi^2_{(df=1)}$ = 17.797 ***p*<0.001*** Odds ratio (95%CI) 5.603 (2.373-13.231)	

n : Number of patients, df: degree of freedom, χ^2 : Pearson Chi-Square, *: Significant**,** CPAP:continuous positive air way pressure

As regards the laboratory investigations, there were no statistically significant differences between the three studied groups at 2 or 4 weeks except for CRP readings at 4 weeks. It showed statistically significant differences between the three studied groups where it was observed that vitamin A group had a higher CRP reading in comparison to the other groups **(Table 4)**.

Table (4): Laboratory investigations of the three studied groups

	Group			Test of Significance *p* value
	Vitamin A (n=62)	**□ blocker (n=62)**	**Judicious O_2(n=62)**	
Hemoglobin (2 weeks) (g/dl) Mean ± S.D. 95% CI for mean	11.84±0.92 11.606-12.072	11.77±1.08 11.501-12.047	11.50±1.19 11.202-11.804	$F_{(df=2)}$= 1.731 *p*= 0.180 NS
Hemoglobin (4 weeks) (g/dl) Mean ± S.D. 95% CI for mean	11.95±1.05 11.686-12.218	11.90±0.96 11.900-11.656	12.09±1.07 11.821-12.363	$F_{(df=2)}$= 0.580 *p*= 0.561 NS
WBCs (2 weeks) (x10^3/mm^3) Mean ± S.D. 95% CI for mean	15.6±3.80 14.508-16.718	13.97±3.17 12.427-15.511	14.76±3.51 12.950-16.579	$F_{(BF)(df=2)}$= 1.176 *p*= 0.311 NS
WBCs (4 weeks) (x10^3/mm^3) Mean ± S.D. 95% CI for mean	11.68±2.73 10.847-12.507	11.68±2.46 11.059-12.309	11.91±2.80 10.946-12.876	$F_{(BF)(df=2)}$= 0.106 *p*= 0.900 NS
Platelets (2 weeks) (x10^3/mm^3) Mean ± S.D. 95% CI for mean	206.31±50.08 193.590-219.321	211.90±46.51 200.093-223.714	208.76±50.76 193.835-223.681	$F_{(df=2)}$= 0.180 *p*=0 .189 NS
Platelets (4 weeks) (x10^3/mm^3) Mean ± S.D. 95% CI for mean	194.81±29.74 187.253-202.360	194.52±30.26 186.831-202.202	199.39±35.15 190.460-208.314	$F_{(df=2)}$= 0.457 *p*=0.634 NS
TSB (2 weeks) (mg/dl) Mean ± SD. 95% CI for mean	5.04±1.21 4.629-5.444	5.30±1.22 4.823-5.278	5.38±1.24 4.936-5.822	$F_{(df=2)}$= 0.655 *p*= 0.520 NS
TSB (4 weeks) (mg/dl) Mean ± SD. 95% CI for mean	3.25±0.80 3.007-3.428	3.26±0.81 2.985-3.526	3.53±0.83 3.235-3.830	$F_{(df=2)}$= 12.485 *p*=0.242 NS
CRP (2 weeks) (mg/L) Mean ± SD. 95% CI for mean	5.90±1.31 5.1406–6.6552	6.92±1.60 6.1658–7.6729	5.84±1.25 5.2653–6.4089	$F_{(df=2)}$= 1.428 *p*=0 .051 NS
CRP (4 weeks) (mg/L) Mean ± Std. Deviation 95% CI for mean	4.11±0.95 3.6556–4.5573	3.89±0.90 3.5542–4.2168	2.91±0.62 2.5931–3.2230	$F_{(df=2)}$= 36.202 ***p*<0.001***
Urea (2 weeks) (mg/dl) Mean ± SD. 95% CI for mean	25.07±6.20 21.635-28.504	22.35±5.32 19.252-25.452	26.73±6.32 24.395-29.057	$F_{(BF)(df=2)}$=2.180 *p*= 0.116 NS
Urea (4 weeks) (mg/dl) Mean ± SD. 95% CI for mean	14.94±3.61 13.711-16.160	14.15±3.48 13.262-15.028	15.44±3.80 13.967-16.920	$F_{(BF)(df=2)}$=1.152 *p*=0 .319 NS
Creatinine (2 weeks) (mg/dl) Mean ± SD. 95% CI for mean	0.69±0.16 0.62-0.75	0.76±0.18 0.69-0.82	0.74±0.17 0.66-0.82	$F_{(df=2)}$=1.039 *p*=0 .356 NS
Creatinine (4 weeks) (mg/dl) Mean ± SD. 95% CI for mean	0.64±0.14 0.58-0.69	0.65±0.15 0.59-0.70	0.61±0.14 0.55-0.66	$F_{(df=2)}$= 0.605 *P*=0.547 NS

Regarding the relation of ROP and laboratory investigations, there were no statistically significant differences between the two studied groups at 2 and 4 weeks (**Table 5)**.

Table (5): Relation of ROP and laboratory investigations

	Retinopathy Overall		Test of Significance *p* value
	No (n=142) (76.34%)	**Yes (n=44) (23.66%)**	
Hemoglobin (2 weeks) (g/dl) Mean ± S.D. 95% CI for mean	11.78±0.13 11.592-11.968	11.47±0.80 11.224-11.708	$t_{(df=184)}$=1.709 *p*<0.001*
Hemoglobin (4 weeks) (g/dl) Mean ± S.D. 95% CI for mean	11.97±1.10 11.786-12.150	12.03±0.76 11.795-12.255	$t_{(W)(df=104.005)}$=0.392 *p=0.*696 NS
WBCs (2 weeks) (x10³/mm³) Mean ± S.D. 95% CI for mean	14.84±3.31 13.925-15.761	14.59±3.12 12.374-16.799	$t_{(W)(df=59.218)}$=0.215 *p=0.*830 NS
WBCs (4 weeks) (x10³/mm³) Mean ± S.D. 95% CI for mean	11.88±2.81 11.338-12.421	11.36±2.63 10.445-12.282	$t_{(df=184)}$=0.932 *p*=0.353 NS
Platelets (2 weeks) (x10³/mm³) Mean ± S.D. 95% CI for mean	209.60 ±50.72 201.192-218.020	207.00±50.42 190.054-223.946	$t_{(df=184)}$=0.291 *p=0.*772 NS
Platelets (4 weeks) (x10³/mm³) Mean ± S.D. 95% CI for mean	197.98±32.66 192.561-203.397	190.00±28.10 182.072-199.155	$t_{(df=184)}$=1.349 *p=0.*179 NS
TSB (2 weeks) (mg/dl) Mean ± SD. 95% CI for mean	5.23±1.41 4.944-5.522	5.26±1.32 4.722-5.796	$t_{(df=184)}$=0.087 *p*=0.931 NS
TSB (4 weeks) (mg/dl) Mean ± SD. 95% CI for mean	3.32±0.81 3.151-3.499	3.41±0.83 3.065-3.760	$t_{(df=184)}$=0.475 *p*=0.635 NS
CRP (2 weeks) (mg/L) Mean ± SD. 95% CI for mean	6.16 ± 1.13 5.67 – 6.64	6.41 ± 1.41 5.70 – 7.10	$t_{(df=184)}$=0.513 *p*=0.608 NS
CRP (4 weeks) (mg/L) Mean ± SD. 95% CI for mean	3.75 ± 0.93 3.48 – 4.01	3.25 ± 0.81 2.84 – 3.64	$t_{(df=184)}$=1.910 *p*=0.002*
Urea (2 weeks) (mg/dl) Mean ± SD. 95% CI for mean	28.9 ± 7.01 26.3 – 31.5	26.4 ± 6.41 22.2 – 30.6	$t_{(W)(df=79.420)}$=1.017 *p=0.*312 NS
Urea (4 weeks) (mg/dl) Mean ± SD. 95% CI for mean	14.7 ± 3.41 13.6 – 15.7	14.5 ± 3.53 12.6 – 16.3	$t_{(df=184)}$=0.199 *p*=0.842 NS
Test of significance (Paired t-test) ***p*- value**	$t_{(df=141)}$ =9.558 ***p*<0.001***	$t_{(df=43)}$ =4.937 ***p*<0.001***	
Creatinine (2 weeks) (mg/dl) Mean ± SD. 95% CI for mean	0.68 ± 0.16 0.63 – 0.73	0.71 ± 0.17 0.60 – 0.82	$t_{(W)(df=61.833)}$=0.457 *p*=0.649 NS
Creatinine (4 weeks) (mg/dl) Mean ± SD. 95% CI for mean	0.58 ± 0.12 0.54 – 0.62	0.60 ± 0.14 0.53 – 0.67	$t_{(df=184)}$=0.505 *p*=0.614 NS

As regards the effect of adding vitamin A and beta blockers to the treatment regimen of ROP: There was a significant association as shown. Those with grade I ROP were the least among newborns who were on β-blockers in comparison to the other groups unlike the grade II ROP, which was the least among those who were on vitamin A in comparison to the other groups. Those who were free of ROP at 2 weeks and became grade I ROP at 4 weeks showed statistically significant differences between the three groups. 100.00% of the cases were in judicious O2 group. Advancement from grade I ROP at 2 weeks to grade II ROP at 4 weeks showed statistically significantly differences between the three groups. 59.09% of these cases were in β-blockers group. Those who were grade I ROP at 2 weeks

and stayed as a grade I at 4 weeks showed statistically significant differences between the three studied groups. 69.23% of the cases were in vitamin A group. **(Table 6)**

Table (6): Effect of group specific treatment plan on overall retinopathy

	Group						Test of significance	P value
	Vitamin A		β-blocker		Judicious O2			
	n	%	n	%	n	%		
Retinopathy Overall								
Yes (n=44)	10	16.13%	14	22.58%	20	32.26%	$X^2_{(df=2)}$= 4.525	P(MC) = 0.108 NS
No (n=142)	52	83.87%	48	77.42%	42	67.74%		
Grade of Retinopathy (2 weeks)								
I (n=35)	10	28.57%	14	40.00%	11	31.43%	$X^{22}_{(df=2)}$ =5.584	P(MC) =0.098
II (n=3)	0	0.00%	0	0.00%	3	100.00%		
Grade of Retinopathy (4 weeks)								
I (n=19)	9	47.37%	1	5.26%	9	47.37%	$x^2_{(df=2)}$= 16.372	**$p_{(MC)}$<0.001***
II (n=25)	1	4.00%	13	52.00%	11	44.00%		
Status of grade of Retinopathy 2W and 4W								
No Retinopathy at 2 Weeks then Grade I at 4 Weeks	0	0.00%	0	0.00%	6	100.00%	$x^2_{(df=2)}$= 8.337	**$p_{(MC)}$=0.023***
Grade I at 2 Weeks and remain Grade I at 4 Weeks	9	69.23%	1	7.69%	3	23.08%	$x^2_{(df=2)}$= 22.965	**$p_{(MC)}$<0.001***
Grade I at 2 Weeks and become Grade II at 4 Weeks	1	4.55%	13	59.09%	8	36.36%	$x^2_{(df=2)}$= 17.486	**$p_{(MC)}$<0.001***
Grade II at 2 Weeks and remain Grade II at 4 Weeks	0	0.00%	0	0.00%	3	100.00%	$x^2_{(df=2)}$= 3.863	$p_{(MC)}$=0.239NS

(MC): Monte Carlo test NS: Statistically non-significant, *

DISCUSSION

Our research found no statistically significant differences among the three groups evaluated for sex, gestational age, birth method, and consanguinity. This was in line with the findings of the study by **Garofoli *et al.* [17],** which concluded that there were no statistically significant differences in terms of sex, gestational age, or delivery method between the analysed groups. They found no statistically significant differences between the studied groups regarding the maternal age, birth weight, and head circumference (P>0.05), were in agreement with our findings that there were no statistically significant differences between the three studied groups regarding the birth weight, head circumference, cardiac anomalies, and skeletal anomalies.

Our study found no statistically significant differences between the three studied groups for maternal age, maternal diabetes, maternal hypertension, or maternal drug intake (P>0.05), which was consistent with the findings of **Garofoli *et al.* [17]** who found no differences between the studied groups for maternal age.

In our investigation, there were no statistically significant differences in the maternal risk variables of maternal age, maternal diabetes mellitus, maternal hypertension, and medications between the infants with ROP and the newborns without ROP groups. **Lepore *et al.* [18]** and **Gilligan *et al.* [19]** conducted matched case-control research with 144 patients (72 patients in the case group and 72 patients in the control group) in contrast to us. Only birth weight and mother age were revealed to be significant risk factors when 66 potential risk variables were examined. Maternal age was substantially higher in the case group compared to the control group (31.2 5.1 years vs. 28.2 5.3 years, P <0.001) and birth weight was significantly lower in the case group (1,248.7 257.8 g vs. 1,335.5 297.2 g, P = 0.01).

Additionally, **Bancalari *et al.* [20]** discovered a correlation between maternal hyperglycemia and ROP, with the intensity of the link growing as ROP severity rose. In a retrospective cohort research, he collected 883 pairs of maternal-neonatal data on newborns under 1500 grammes. 72 (8.2%) of the 883 mothers had DM. According to the multivariate analysis's findings, maternal diabetes and severe ROP (grade 3 or above) are positively associated in a statistically significant manner. In general, the likelihood of a diabetes woman giving birth to a child with severe ROP is 3.5 times greater than the likelihood of a non-diabetic mother (OR: 3.47 [95% CI: 1.51-7.96]; P=0.01).

Alshaikh *et al.* [21] did a retrospective cohort analysis with children delivered to moms with pre-eclampsia. Of the 185 newborns in the normotensive group, 50 (27%) and the 97 infants in the pre-eclampsia group, 27, respectively, had ROP. Pre-eclampsia was not found to be a risk factor for the development of ROP in multivariable regression modelling (OR 1.4, 95% CI 0.46 to 4.1 P>0.05).

According to our research, there were no statistically significant differences between the three groups in terms of the newborn risk variables free oxygen, continuous positive airway pressure (CPAP), mechanical ventilation, and blood transfusion. This was in line with the findings of **Garofoli *et al.* [17],** who discovered no statistically significant variations in mechanical ventilation across the groups under study.

In our investigation, there was a statistically significant relationship between ROP and O_2 usage in either invasive or non-invasive (free O_2) approaches (mechanical ventilation). There was no statistically significant correlation with CPAP, and 86.36% of individuals with ROP required mechanical ventilation (P<0.001), 0.0% required free O_2 (P<0.001), and 0.0% required neither (P<0.001). Additionally, a statistically significant link between blood transfusion and ROP was found (P<0.001). A blood transfusion was required by 34.09% of ROP patients. According to **Akkawi *et al.* [22]** the incidence of ROP among newborns who received surfactant was not statistically significant (P= 0.65).

They discovered that using either mechanical ventilation (P= 0.007) or non-mechanical CPAP or nasal cannula is substantially linked with the development of ROP (P 0.001). Unlike us, **Chaudhari *et al.* [23]** discovered that CPAP was strongly linked to the emergence of ROP. Additionally, **Bancalari *et al.* [20]** conducted a meta-analysis of 2628 identifiable records, 18 studies, 15072 preterm babies, and 5620 instances of ROP, and found that RBC transfusion is an independent risk factor for the development of ROP. RBC transfusion was found to be substantially linked with ROP (pooled OR = 1.50, 95% CI: 1.27-1.76) using a random effect model. In the group with a gestational age (GA) 32 weeks, RBC transfusion was more closely associated with ROP (OR = 1.77, 95% CI: 1.29-2.43) than it was in the group with a GA 34 weeks (OR = 1.36, 95% CI: 0.85-2.18).

According to the current study, there were no statistically significant variations between the two groups' CRP, urea, creatinine, hemoglobin, WBCs, and platelets. This was in line with the findings of a research by **Omotoso *et al.* [24]** who discovered no statistically significant variations in the levels of CRP, urea, and creatinine between the two groups under study (P=0.116).

On the other hand, **Stutchfield *et al.* [25]** found that, children who did not develop ROP had higher initial hemoglobin levels (on admission) than infants who did (27%; P=0.009). The progression of grade I ROP to grade II ROP happened substantially less often among individuals in the vitamin A group (4.55%) compared to the beta blockers group (59.09%) and the prudent O_2 group (36.36%) in our research (P<0.001).

The progression of grade I ROP to grade II ROP happened substantially less often among individuals in the vitamin A group (4.55%) compared to the beta blockers group (59.09%) and the prudent O_2 group (36.36%) in our research (P=0.000). Low plasma vitamin A concentrations have been linked to the emergence of ROP, and aberrant conjunctival impression cytology has been linked to ROP needing therapy, according to research by **Mactier and Weaver [26]**. A non-significant trend towards a decrease of ROP in newborns receiving vitamin A supplements was seen in the forty-four pooled data.

The complicated pathophysiology of ROP involves oxidative damage to the developing retina caused by free radicals, which might theoretically be mitigated by vitamin A's antioxidant qualities. ROP has a negative impact on the growth of photoreceptors; it is uncertain if this is regulated by the availability of vitamin A and/or rhodopsin. In a group of ELBW babies who got 10,000 IU injectable vitamin A three times a week, the incidence of threshold ROP (> 3ROP grade) was zero, as opposed to 16% in those who received half this amount.

It is possible that larger vitamin A dosages than those linked to better respiratory outcomes in preterm children will reduce the incidence of ROP, even if this result did not reach statistical significance. In agreement with our findings, **Bührer *et al.* [27]** carried out two small bicentric, pilot, randomised controlled trials using oral propranolol (starting dose: 0.5 mg/kg/day, divided into 3 doses, incrementally increased to 1.5 mg/kg/day) and discovered a non-significant decrease in ROP necessitating intervention by laser treatment or bevacizumab injection of comparable magnitude. In all, ROP was performed on 6 of 35 babies who were receiving oral propranolol (17%) as opposed to 14 of 36 controls (39%) (relative risk 0.42, 95% CI: 0.15-1.16).

CONCLUSIONS

Vitamin A has an important role in decreasing the morbidity and mortality among the newborns. Prophylactic high dose of vitamin A (1500 IU/day as early as possible) in high-risk neonates may help reduce the incidence and severity of ROP. Also, the administration of oral propranolol (0.5-2 mg/kg/day) may be effective in counteracting the progression of ROP, but its safety is a concern.

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