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Research Article

Vitamin-A In Retinopathy Prevention: A Study on Preterm Babies

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Abstract

Background: Vitamin A -retinoids and their active metabolite, retinoic acid has highly potent antiangiogenic activity by inhibiting VEGF expression at the neovascularization phase.

Objectives: To evaluate preventive effect of vitamin A on ROP.

Materials and method: This randomized controlled trial study was conducted in the Neonatology Department of Dhaka Shishu Hospital among the preterm neonates of 32-34 completed weeks of gestation and also those neonates whose 1st ROP screening showed peripheral avascular zone irrespective of gestational age from July 2018 to June 2020. Initially 228 preterm neonates were enrolled in this study. Among them 164 preterm neonates were randomly allocated in vitamin A group (82) and control group (82). Vitamin A group received vitamin A drop perorally (5000 IU/Kg/day), added to their enteral feeds as soon as minimal feeding was introduced and continued from starting point to 4 weeks and dose of vitamin A also adjusted with multivitamin drop when vitamin A group had to be given multivitamin drop. Control group had been given multivitamin drop from 2 weeks of age. Out of these, 6 neonates died, 1 neonate shifted to another hospital and 9 neonates did not come for follow up after discharge. So finally, 148 neonates were completed this study.

Results: Stage 1 ROP was equal in both groups in first follow up. In subsequent second and third follow up stage 2 ROP and stage 3 ROP was significantly higher in control group than vitamin A group (55.6% vs 23.7%) and (41.7% vs 19.7%) respectively. In terms of zones, zone-I ROP (which is worst condition) found significantly higher in control group than vitamin A group (56.9% vs 27.6%) in third follow up. In case of plus disease, at third follow up it had been found higher number in control group than vitamin A group (56.9% vs 27.6%). In overall it was found that incidence of ROP was reduced in vitamin A group in contrast to control group (32.9% vs 59.7%). In present study, rate of ROP 32.9% in vitamin A group and 59.7% in control group.

Conclusion: Vitamin A supplementation prevents retinopathy of prematurity in preterm babies.

Key words: vitamin a; retinopathy of prematurity; pre-term baby

Introduction

Retinopathy of prematurity (ROP) is a disorder of the developing retina in preterm newborns and is a leading cause of preventable childhood blindness. WHO Health Organization's Vision 2020 program has recognized retinopathy of prematurity as an important cause of childhood blindness in industrialized and developing countries. In Dhaka Shishu Hospital (DSH) two studies reported that the incidence of ROP was 35% (Saha et al., 2017) and 40% (Akter et al., 2010) respectively. Bangladesh is a highly populated country with high birth rate and high incidence of premature delivery (14%). Preterm babies of <34 weeks are at high risk for ROP. The incidence of ROP varies from 10-46% among the preterm infants. In our country incidence of ROP ranges from 35-40% among the preterm infants. Ophthalmological examinations of the preterm babies are not available everywhere in Bangladesh and many of the preterm babies do not come for routinely eye examinations. Prevention of ROP is very important in terms of ROP morbidity which affect quality of life, independence and worsen mental health, cognition and educational attainment. There are some studies done in abroad showed that incidence of ROP can be reduced by giving early vitamin A to preterm baby. So far, it was known that there is no related study done

in our country. Therefore, this study has been conducted to evaluate the preventive role of vitamin A on ROP in preterm baby.

Methods

Study design was randomized controlled trial and study duration was July 2018 to June 2020 at Neonatal Ward, Dhaka Shishu Hospital among all preterm babies admitted in neonatal ward of Dhaka Shishu Hospital during the study period. Data were collected using a structured questionnaire (research instrument) containing all the variables of interest. A standard questionnaire including cardinal points of the history, examination findings and pre & post medication investigation results prepared by the investigator was used to collect data. Sample was collected by simple random sampling and randomization was done by lottery method. At first 8 sealed envelopes were kept in a small box at a time, 4 containing name of study group in a paper inside and 4 of control group. One envelope was randomly opened during enrolment and the case was assigned to that group. This process was repeated until expected number of samples were enrolled. After admission of preterm neonates in SCABU and NICU were assessed by modified new ballard scoring and history of last menstrual period (LMP) for gestational age. Preterm neonates who were between 32-34 weeks and also those neonates whose 1st ROP screening showed peripheral avascular zone were selected. The parents or guardians of the neonates who met the inclusion criteria were informed about retinopathy of prematurity. They were also explained about the purpose, procedure, importance and benefit of the study. Informed written consent was secured from them and then enrollment was done. After enrollment, baseline assessment was done and subjects were randomized by block randomization on a 1:1 basis to either the active treatment or control arm. In vitamin A supplementation group, preterm infants were given the daily dose of 5000 IU/Kg/day vitamin A drop perorally as soon as enteral feeding was started and continued from starting point to 4 weeks. Vitamin A was given by insulin syringe as Cap. Ratinol Forte, marketed by Drug International, Bangladesh. DAR (Drug administration Registration) no (210-47-078), Mfg. Lic. (Manufacturing license) no (127 & 389) and expired date of drug ensured before giving drug. Each capsule of Ratinol Forte contains 50,000 IU retinyl palmitate. At first, squeezed vitamin A capsule (50000 IU) and made sure the entire content fell into the insulin syringe of 100 unit and upto 20 unit of insulin syringe filled with vitamin A. So each unit of insulin syringe contained 2500 IU vitamin A. Multivitamin drop was started from 2 weeks of age in both groups. In case of vitamin A group multivitamin drop was given as drop V-plex perorally along with vitamin A capsule and dose of vitamin A adjusted with multivitamin drop. Each ml of V-plex drop contain 5000 IU vitamin A along with other vitamins. Dose of vitamin A also adjusted with multivitamin drop when vitamin A group had to be given multivitamin drop. Control group had been given standard treatment and multivitamin drop from 2 weeks of age. Daily follow up regarding clinical course, oxygen supplementation along with other complication like respiratory distress syndrome, asphyxia, apnea, hyper bilirubinemia and septicemia were recorded in the questionnaire. On every Thursday, ROP screening was done in our NICU ward. During discharge I counselled both groups for ROP screening and contacted with them over phone. I ensured their 1st ROP screening which was done at 4 weeks of age. First ROP screening was done at 4 weeks of age. It was performed by Associate Professor Dr. Shamima Jahan and researcher assisted her. Pupils were dilated with 0.5% tropicamide eye drops and was instilled twice 1 to 5 minutes apart. The examination was performed 20 to 25 minutes later using a binocular indirect ophthalmoscope and +20D lens. Follow up schedule was planned according to location and severity of ROP. One week follow up: zone I stage 1 or 2 ROP and two weeks follow up: zone II stage 1 ROP. Lowest the zone and highest the stage of ROP considered as highest risk for severe ROP. Patient who had ROP, classified into stage (1-5), zone (I-III) and presence or absence of plus disease. Findings were analyzed between vitamin A and control group. Preterm neonates whose ROP screening showed zone I any stage with plus disease or zone I stage 3 without plus disease or zone II stage 2 or 3 with plus disease assigned for laser therapy or intravitreal anti VEGF therapy (Bevacizumab) or combination of both. Regression of ROP in any stage and any zone were noted and follow up of every 1-2 weeks was carried out up to 45 weeks of post menstrual age.

Figure 1: Indirect ophthalmoscope

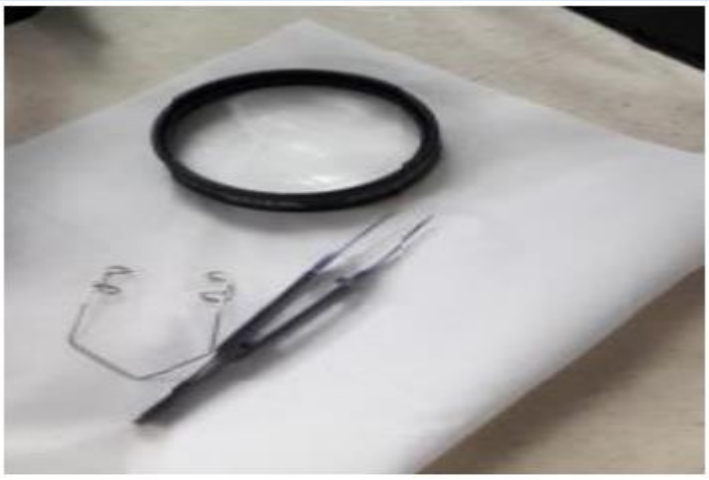
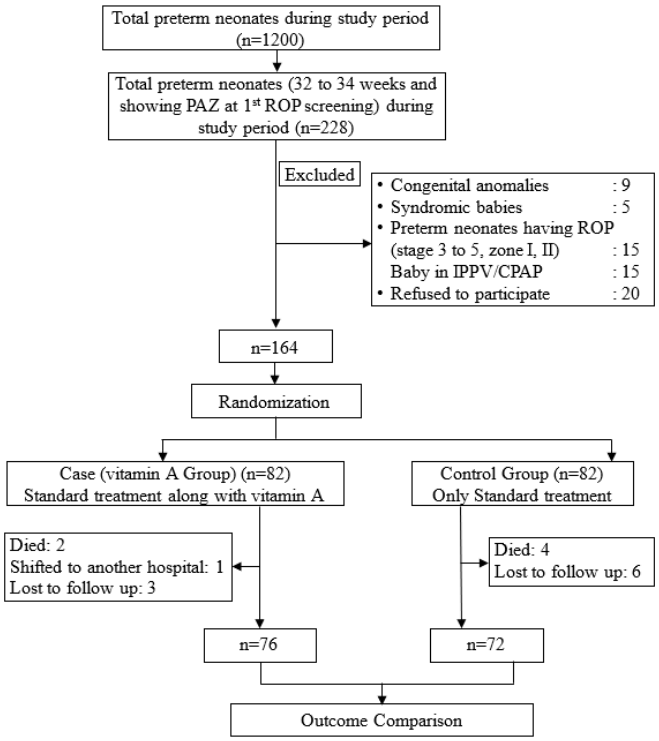


Figure 2: 20D condensing lens and speculum used for screening.

Study Flow Chart



Zones of retinopathy: The zones are centered on the optic nerve.

- Zone I is the posterior of the retina, defined as the circle with a radius extending from the optic nerve to double the distance to the macula.
- Zone II is an annulus with the inner border defined by zone I and the outer border defined as the distance from the optic nerve to the nasal oraserrata.
- Zone III is the residual temporal crescent of the retina.

Stages of retinopathy: Description of the ophthalmoscope findings at the junction.

- Stage 1 is a fine demarcation.
- Stage 2 is an elevated ridge.
- Stage 3 is extraretinal fibrovascular tissue.
- Stage 4 is subtotal retinal detachment.
- Stage 5 is total retinal detachment.

Plus disease presence of dilatation and tortuosity of retinal vessels at posterior pole of eye. Also associated with papillary rigidity and vitreous haze.

In this study stage 2 or more ROP and zone I or II ROP and presence of plus disease has been considered as significant ROP.

Results

Age group (hours) Enrolled at hospital admission	Case (Vitamin A) (n=76) n (%)	Control (n=72) n (%)	p-value
<24	42(55.3)	35(48.6)	0.447 ns
24-48	6(7.9)	8(11.1)	0.916 ns
48-72	10(13.2)	14(19.4)	0.245 ns
Age group (days) Enrolled after 1st ROP screening			
≥28	18(23.7)	15(20.8)	0.190 ns
Mean±SD	54.2±45.6	55.8±48.4	0.838ns

Table I: Age distribution of study population in two groups (n=148).

Table I shows no significant difference of age on enrollment between two groups. Mean age of vitamin A group were 54.2 ± 45.6 hours and control group were 55.8±48.4 hours. Vitamin A group (76.3%) and control group (79.2%) enrolled at hospital admission (<72 hours age group). Vitamin A group (23.7%) and control group (20.8%) were enrolled after 1st ROP screening (≥28 days age group).

Sex	Case (Vitamin A) (n=76) n (%)	Control (n=72) n (%)	p-value
Male	40(52.6)	45(62.5)	0.225^{ns}
Female	36(47.4)	27(37.5)	
Total	76(100.0)	72(100.0)	

Table II: Sex distribution of study population in two groups (n=148).

Table II shows in vitamin A and control group male and female were in equal distribution. No

significant association of sex between two groups.

Stages of ROP	Case (Vitamin A) (n=76) n (%)	Control (n=72) n (%)	p-value
1st follow up			
Stage-1	67(88.2)	64(88.9)	0.889^{ns}
Stage-2	9(11.8)	8(11.1)	
2nd follow up			
Stage-1	55(72.4)	30(41.7)	<0.001***
Stage-2	18(23.7)	40(55.6)	
Stage-3	3(3.9)	2(2.8)	
3rd follow up			
Stage-1	55(72.4)	30(41.7)	<0.001***
Stage-2	6(7.9)	12(16.7)	
Stage-3	15(19.7)	30(41.7)	

Table III: Comparison of stages of ROP findings in two groups (n=148) in different follow up.

Table III shows at 1st follow up no significant association was found in stages between two groups. At 2nd and 3rd follow up stage 2 ROP and stage 3 ROP was highly significantly (p<0.001) increased in control group compared to vitamin A group.

Zones of ROP	Case (Vitamin A) (n=76) n (%)	Control (n=72) n (%)	p-value
1st follow up			
Zone-I	1(1.3)	1(1.4)	0.969^{ns}
Zone-III	75(98.7)	71(98.6)	
2nd follow up			
Zone-II	19(25.0)	40(55.6)	<0.001***
Zone-III	57(75.0)	32(44.4)	

3rd follow up			
Zone-I	21(27.6)	41(56.9)	<0.001***
Zone-III	55(72.4)	31(43.1)	

Table IV: Comparison of zones of ROP findings in two groups (n=148) in different follow up.

Table IV shows at 1st follow up no significant association was found in zone between two groups. At 2nd and 3rd follow up zone-2 ROP and zone-III ROP was highly significantly (p<0.001) increased in control group compared to vitamin A group.

Plus Disease	Case (Vitamin A) (n=76) n (%)	Control (n=72) n (%)	p-value
1st follow up			
Present	1(1.3)	1(1.4)	1.000ns
Absent	75(98.7)	71(98.6)	
2nd follow up			
Present	2(2.6)	3(4.2)	0.605ns
Absent	74(97.4)	69(95.8)	
3rd follow up			
Present	21(27.6)	41(56.9)	<0.001***
Absent	55(72.4)	31(43.1)	

Table V: Comparison of plus disease in two groups (n=148) in different follow up.

Table V shows at 1st and 2nd follow up, no significant association was found in plus disease between two groups. In 3rd follow up plus disease was highly significantly (p<0.001) higher in control group compare to vitamin A group.

Comments by ophthalmologist	Case (Vitamin A) (n=76) n (%)	Control (n=72) n (%)	p-value
1st follow up			
No ROP	68(89.5)	67(93.1)	0.442ns
ROP	8(10.5)	5(6.9)	
2nd follow up			
No ROP	56(73.7)	35(48.6)	0.002**
ROP	20(26.3)	37(51.4)	
3rd follow up			
No ROP	51(67.1)	29(40.3)	0.001**
ROP	25(32.9)	43(59.7)	

Table VI: Comparison of occurrence of ROP between two groups (n=148) in different follow up.

Table-VI shows at 1st follow up no significant association was found in ROP between two groups. At 2nd and 3rd follow up ROP was highly significantly (p<0.001) increased in control group compared to vitamin A group.

Discussion

Retinopathy of prematurity (ROP) is a potentially preventable cause of blindness. To control blindness due to ROP there is an urgent need to increase awareness among the public, health professionals and parents. Gilbert et al (2008) demonstrated that premature infants in the developing countries are at most risk of having severe ROP. This randomized controlled trial study was conducted in the Department of Neonatology of Dhaka Shishu Hospital in Bangladesh to find out the effect of vitamin A supplementation in preterm babies to prevent ROP. Vitamin A exerts highly potent antiangiogenic activity by inhibiting VEGF expression. Vitamin A supplementation may prevent neovascularization resulting from oxygen-induced retinopathy by down regulating VEGF expression. Thus, vitamin A treatment may be a safe choice in the clinical practice for ROP prevention. In this study, age on enrollment between two groups was similar and statistically not significant (p>0.05). Vitamin A group (76.3%) and control group (79.2%) enrolled at hospital admission (<72 hours age group). Vitamin A group (23.7%) and control group (20.8%) were enrolled after 1st ROP screening (≥28 days age group). Sun et al., (2017) in their study showed maximum study population were enrolled <72 hours, which is similar to this study finding. Early vitamin A supplementation reduce risk of ROP in preterm baby (Sun et al., 2017). In present study, in vitamin A group and control group male and female were in equal distribution which was consistent with the study of Garofoli et al., (2020). The screened stages and zones are the most important parameter for detection of situation of ROP. International classification of ROP (ICROP) 1984 and a modification in 1987 takes into account three major aspects of the disease-its location, extent and severity (zone I-III and stage 1-5). Zone I and stage 3 being the highest risk for severe ROP. Stage-1 ROP was equal in both groups in first follow up. In subsequent second and third follow up stage 2 ROP and stage 3 ROP was significantly higher in control group than vitamin A group (55.6% vs

23.7%) and (41.7% vs 19.7%) respectively. In terms of zones, zone-II ROP and zone-I ROP (which is worst condition) found significantly higher in control group than vitamin A group (55.6% vs 25.0%) and (56.9% vs 27.6%) in second and third follow up respectively. This study showed in case of plus disease, at third follow up it had been found higher number in control group than vitamin A group (56.9% vs 27.6%). In our study, in case of vitamin A group, 23 preterm neonates develop ROP. Among them 2 spontaneously recovered and 21 required treatments (5 received retinal laser photocoagulation therapy and 16 was treated by anti-VEGF). In case of control group, 43 preterm neonates develop ROP. Among them 2 spontaneously recovered and 41 required treatments (15 received retinal laser photocoagulation therapy, 16 was treated by anti-VEGF drugs and 10 was needed laser treatment after anti-VEGF therapy). In present study, rate of ROP 32.9% in vitamin A group and 59.7% in control group. So, incidence of ROP was reduced in vitamin A group in contrast to control group. Similar result was found by Sun et al., (2019) and Garofoli et al., (2020). In this study, vitamin A was given orally. Oral formulation is well tolerated and no adverse effects of vitamin A supplementation like bulging fontanelles, vomiting, diarrhea, loss of appetite and irritability had been observed.

Conclusion:

Oral vitamin A supplementation in preterm baby prevents retinopathy of prematurity but could not prevent ROP in preterm babies who got blood transfusion. Vitamin A supplementation causes significant reduction of ROP in preterm babies with oxygen therapy but rate of ROP with oxygen therapy is high.

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