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Role of Vitamin-A regarding Prevention of Retinopathy of Prematurity among Pre-term Babies

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Abstract

Background: Retinopathy of prematurity (ROP) is a Vasoproliferative disorder of the eye affecting preterm infants and is a leading cause of preventable blindness. 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:*** This paper shows oxygen therapy 53.9% in vitamin A group and 76.4% in control group with highly significant ($p<0.01$) difference found between two groups. Septicemia 36.8% in vitamin A group and 55.6% in control group with significant ($p<0.05$) difference found between two groups. Study shows ROP present 48.8% in vitamin A group with oxygen therapy and 78.2% in control group with oxygen therapy which was statistically highly significant ($p<0.01$). Research shows ROP present 64.3% in vitamin A group with septicemia and 85% in control group with septicemia which was statistically significant ($p<0.05$). ***Conclusion:*** Vitamin A supplementation prevents retinopathy of prematurity in preterm babies.

Keywords: Vitamin A; Retinopathy of prematurity; Pre-term baby

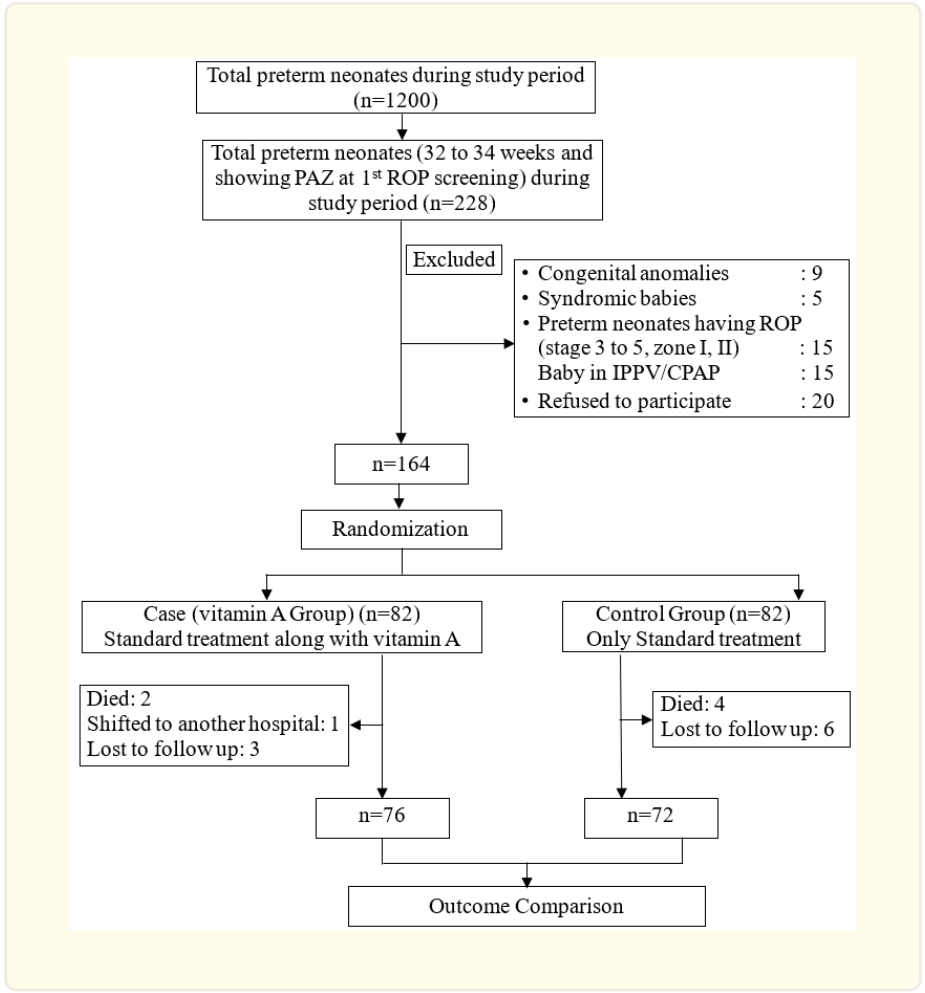
Introduction

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.

Study Flow Chart



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

Table-1 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)	0.225ns
Female	36(47.4)	27(37.5)	
Total	76(100.0)	72(100.0)	

Table 2: Sex distribution of study population in two groups (n=148).

Table-2 shows in vitamin A and control group male and female were in equal distribution. No significant association of sex between two groups.

Antenatal and natal history	***Case (Vitamin A) (n=76) n (%)***	***Control (n=72) n (%)***	***p-value***
Parity			
Primi	53(69.7)	51(70.8)	0.884^{ns}
Multi	23(30.3)	21(29.2)	
Pregnancy type			
Single pregnancy	68(89.5)	63(87.5)	0.707^{ns}
Twin pregnancy	8(10.5)	9(12.5)	
Maternal HTN	24(31.6)	19(26.4)	0.487^{ns}
APH	2(2.7)	4(5.6)	0.376^{ns}
Prolong rupture of membrane	26(34.2)	30(41.7)	0.350^{ns}
Eclampsia/preeclampsia	3(3.9)	1(1.4)	0.337^{ns}
Place of delivery			
Home	15(19.7)	14(19.4)	0.964^{ns}
Hospital	61(80.3)	58(80.6)	
Mode of delivery			
Normal delivery	41(53.9)	39(54.2)	0.979^{ns}
Caesarean section	35(46.1)	33(45.8)	
Gestational age (in weeks)			
29-30	9(11.8)	12(16.7)	0.699^{ns}
31-32	24(31.6)	21(29.2)	
33-34	43(56.6)	39(54.2)	
Birth weight (in gm)			
1500-2000	48(63.2)	36(50.0)	0.106^{ns}
1000-1499	28(36.8)	36(50.0)	

Table 3: Distribution of study population by antenatal and natal history in two groups (n=148).

Table-3 shows considering antenatal and natal history, there is no significant association between two groups. Gestational age was similar in between two groups and was not statistically significant. Gestational age of preterm neonates enrolled after hospital admission was 32-34 weeks and after ROP screening was 29-34 weeks. Birth weight was similar in between two groups and was not statistically significant.

Presenting complaints	***Case (Vitamin A) (n=76) n (%)***	***Control (n=72) n (%)***	***p-value***
Respiratory distress	41(53.9)	47(65.3)	0.161^{ns}
Hypothermia	11(14.5)	13(18.1)	0.555^{ns}
Clinical features of sepsis on admission	3(3.9)	2(2.8)	0.706^{ns}
H/O Apneic attack	1(1.3)	4(5.6)	0.154^{ns}
Perinatal asphyxia	5(6.6)	6(8.5)	0.666^{ns}

Table 4: Distribution of study population by presenting features on first enrollment in two groups (n=148).

Table-4 shows there is no significant difference of presenting complaints between vitamin A and control group.

Risk factors	***Case (Vitamin A) (n=76) n (%)***	***Control (n=72) n (%)***	***p-value***
Oxygen therapy	41(53.9)	55(76.4)	0.004**
Apnea	3(4.0)	2(2.8)	0.683^{ns}
Bag and mask	13(17.6)	13(17.6)	1.000^{ns}
Blood transfusion	18(24.3)	29(39.2)	0.052^{ns}
RDS	9(11.8)	4(5.6)	0.384^{ns}
Septicemia	28(36.8)	40(55.6)	0.022*
Hypoglycemia	1(1.3)	0(0.0)	0.329^{ns}

Table 5: Distribution of study population by risk factors in two groups (n=148).

Table-5 shows oxygen therapy 53.9% in vitamin A group and 76.4% in control group with highly significant ($p<0.01$) difference found between two groups. Blood transfusion 24.3% in vitamin A group and 39.2% in control group which was statistically not significant. Septicemia 36.8% in vitamin A group and 55.6% in control group with significant ($p<0.05$) difference found between two groups.

Group	***ROP***		***p-value***
	Present	***Absent***	
Case (Vitamin A) (n=41)	20 (48.8%)	21 (51.2%)	0.003**
Control (n=55)	43 (78.2%)	12 (21.8%)	

Table 6: Comparison of association of oxygen therapy with ROP between vitamin A and control group (n=148).

Table-6 shows ROP present 48.8% in vitamin A group with oxygen therapy and 78.2% in control group with oxygen therapy which was statistically highly significant ($p<0.01$).

Group	*ROP*		*p-value*
	Present	*Absent*	
Case (Vitamin A) (n=19)	17 (89.5%)	2 (10.5%)	0.705^{ns}
Control (n=28)	24 (85.7%)	4 (14.3%)	

Table 7: Comparison of association of blood transfusion with ROP between vitamin A and control group (n=148).

Table-7 shows ROP present 89.5% in vitamin A group with blood transfusion and 85.7% in control group with blood transfusion which was statistically not significant.

Group	*ROP*		*p-value*
	Present	*Absent*	
Case (Vitamin A) (n=28)	18 (64.3%)	10 (35.7%)	0.047*
Control (n=40)	34 (85%)	6 (15%)	

Table 8: Comparison of association of septicemia with ROP between vitamin A and control group (n=148).

Table-8 shows ROP present 64.3% in vitamin A group with septicemia and 85% in control group with septicemia which was statistically significant ($p<0.05$).

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. 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). In current study, considering antenatal and natal history, there was no significant association was found between two groups. Gestational age was similar in between two groups and was not statistically significant. Gestational age of preterm neonates enrolled after hospital admission was 32-34 weeks and after ROP screening was 29-34 weeks. Birth weight was similar in between two groups and was not statistically significant. Saha et al., (2017) showed development of ROP was inversely proportional to gestational age and birth weight. In this study gestational age and birth weight were similar in vitamin A and control group and statistically not significant. In present study, clinical presentation like respiratory distress, hypothermia, perinatal asphyxia, C/F of sepsis on admission and H/O apneic attack were similar in both groups. Similar findings were found by Garofoli et al., (2020). Oxygen therapy 53.9% in vitamin A group and 76.4% in control group with significant difference was found between two groups. Blood transfusion 24.3% in vitamin A group and 39.2% in control group which was statistically not significant. Septicemia 36.8% in vitamin A group and 55.6% in control group with significant difference was found between two groups. Oxygen therapy, blood transfusion and septicemia were risk factor for ROP. (Akter et al., 2010, Hakeem et al., 2012 and Das et al., 2014). To see the effectiveness of vitamin A in reduction of ROP with these risk factors, comparisons were done between vitamin A and control group individually. Our study showed there was significant decrease incidence of ROP in vitamin A group with oxygen therapy in comparison to control group with oxygen therapy. Das et al., (2014) showed in their study oxy-

gen therapy is individual risk factor for ROP occurrence. This current study showed that ROP occurrence in vitamin A group with blood transfusion is 89.5% and in control group with blood transfusion is 85.7% which was not statistically significant. Akter et al., (2010) showed in their study that blood transfusion is individual risk factor for ROP occurrence. In current study, vitamin A supplementation did not show any significant improvement of ROP in blood transfused preterm baby. This study showed incidence of ROP significantly decreased in vitamin A group with septicemia in comparison to control group with septicemia. Huang et al., (2018) showed in their study immunomodulatory effect of vitamin A to prevent infection. 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

Vitamin A supplementation causes significant reduction of ROP in preterm babies with oxygen therapy but rate of ROP with oxygen therapy is high. Retinopathy of prematurity is a potentially preventable cause of blindness especially in developing countries. From this study we can recommend vitamin A in preterm baby to prevent ROP. A multicentered randomized control study with larger sample size may give better results.

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