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ROLE OF VITAMIN A IN PREVENTION OF RETINOPATHY OF PREMATURITY IN EXTREMELY AND EARLY PRETERM NEONATES

Paediatric Medicine

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ABSTRACT

Background: Retinopathy of prematurity (ROP) is a vaso-proliferative retinal disorder that primarily affects premature infants. In India, the prevalence of ROP in preterm babies ranges from 35% to 60%. Risk factors include low gestational age, low birth weight, sepsis, prolonged high-concentration oxygen therapy, blood transfusions, surfactant use, and intraventricular hemorrhage. While preventive measures remain limited, some studies suggest early vitamin A supplementation may reduce ROP risk by down regulating vascular endothelial growth factor (VEGF), thus preventing oxygen-induced retinal neovascularization. **Objective:** To evaluate the role of vitamin A supplementation in preventing ROP in extremely and early preterm neonates, and to assess the correlation between ROP severity and both the mode and duration of oxygen therapy. **Methods:** This prospective interventional study included 54 neonates born before 34 weeks of gestation, admitted to the neonatal intensive care unit at AJIMS, Mangalore, from March 2021 to December 2022. Neonates were randomized into two groups: the intervention group received oral vitamin A (3000 IU/kg/day) starting with minimal enteral feeding for 28 days, while the control group did not receive vitamin A. All infants received routine NICU care, and ROP screening was performed by a qualified ophthalmologist, with classification based on international ROP criteria. **Results:** Of the 54 neonates, 28 (51.9%) were male and 26 (48.1%) female; 12 (22.2%) were very preterm and 42 (77.8%) moderate preterm. No significant differences in baseline characteristics were found between groups. The incidence of any stage of ROP was significantly higher in the control group compared to the vitamin A group (p=0.0001). Vitamin A supplementation was also associated with a reduced risk of severe ROP (p=0.023). The duration of oxygen therapy significantly influenced ROP incidence, with differences observed for oxygen therapy under and over two days (p=0.013, p=0.16). **Conclusion:** Vitamin A supplementation appears to decrease the incidence and progression of ROP in preterm neonates, suggesting a protective effect against the condition.

KEYWORDS

Retinopathy of prematurity, vitamin A, preterm neonates, vascular endothelial growth factor. (ROP- Retinopathy of Prematurity, VEGF- Vascular Endothelial Growth Factor)

INTRODUCTION

Retinopathy of Prematurity (ROP) is a significant retinal disorder that primarily affects preterm infants, leading to visual impairment and blindness. It is a vasoproliferative condition characterized by abnormal growth of retinal blood vessels, which can potentially result in retinal detachment and loss of vision[1]. ROP remains a prevalent concern worldwide and contributes significantly to childhood blindness, particularly in developing countries. Despite advancements in neonatal care, the prevalence of ROP continues to be high, especially among extremely preterm and very low birth weight infants[2]. The pathogenesis of ROP is complex and involves multiple factors, including gestational age, birth weight, supplemental oxygen exposure, and systemic health conditions, among others[3].

The development of ROP is associated with disrupted retinal vascularization, which occurs in two distinct phases. The initial phase involves the arrest of normal blood vessel growth due to premature birth and exposure to high levels of oxygen therapy, leading to hyperoxia-induced downregulation of vascular endothelial growth factor (VEGF)[4]. This phase is followed by a subsequent phase of hypoxia-induced pathological neovascularization, during which there is an upregulation of VEGF and other growth factors in response to retinal ischemia. This abnormal blood vessel growth may lead to fibrosis, hemorrhage, and in severe cases, retinal detachment. The role of VEGF, along with insulin-like growth factor-1 (IGF-1), is critical in the development of ROP, as these factors regulate the growth and differentiation of retinal blood vessels[5]. Targeted inhibition of VEGF during the neovascular phase can potentially prevent or reduce the extent of destructive neovascularization, thereby minimizing the risk of severe ROP and subsequent visual impairment[6].

Although screening programs and interventions such as laser photocoagulation and anti-VEGF injections have improved outcomes, ROP remains a significant cause of morbidity due to the lack of definitive preventive therapies[7]. The current treatments, primarily targeting advanced stages of ROP, often have limited success in improving long-term visual outcomes. The need for an effective preventive strategy to minimize the onset and progression of ROP is evident, particularly in low-resource settings where access to advanced treatments may be limited[8].

Vitamin A is a crucial micronutrient for visual function, playing a key role in the maintenance of normal vision and the development of the retina. In preterm infants, plasma retinol levels are often low, reflecting inadequate hepatic stores, thus increasing their susceptibility to ROP. Vitamin A has been shown to have potential protective effects against oxygen-induced retinopathy by modulating the expression of VEGF and reducing oxidative stress[9]. Early supplementation with vitamin A may help prevent the onset and progression of ROP by promoting the maturation of retinal vasculature and preventing aberrant neovascularization. Several studies have suggested a beneficial effect of vitamin A supplementation in reducing the incidence and severity of ROP, although evidence remains inconclusive due to variations in study design and dosing regimens[9–11].

Objectives of the Study

- **Primary Objective: -** To compare ROP staging in early and extremely preterm neonates receiving oral vitamin A supplementation with ROP staging of early and extremely premature neonates not receiving oral vitamin A supplementation
- **Secondary Objective: -** To correlate the stage of ROP with mode of oxygen delivery and duration of oxygen therapy

MATERIALS AND METHODS

Study Design and Setting

A prospective interventional study was conducted on neonates born before 34 completed weeks of gestation and admitted to the neonatal intensive care unit (NICU) at A J Institute of Medical Sciences (AJIMS), Mangalore. The study period spanned from March 2021 to December 2022.

Inclusion and Exclusion Criteria

The study included neonates born before 34 weeks of gestation. Exclusion criteria encompassed neonates with congenital TORCH infections, genetic metabolic disorders, congenital ocular abnormalities, major congenital malformations, and abnormal umbilical artery blood flow.

Parental Consent: Before randomization, informed written consent was obtained by either parent of the neonates to be enrolled in the study. In all the newborns, relevant information was collected in a predesigned proforma.

Randomization and Intervention

Participants were randomized into two groups using the odd-even method. The interventional group (Group B) received oral vitamin A (3000 IU/kg/day), starting with minimal enteral feeding and continuing for 28 days. The control group (Group A) received standard NICU care without vitamin A supplementation.

Vitamin-a Supplementation: Vitamin A (Indian medicine: 500000 IU/1mL) is used in the study. Study group neonates were administered oral vitamin A, 3000 IU/kg/day when minimal enteral feeding was started with orogastric tube (OGT) and continued for 28 days[11]. If the neonate vomited within 5 minutes, dose was repeated[12]. If child was being discharged before 28 days of vitamin A supplementation, caretaker was taught the technique of giving vitamin A at home. Control group infants did not receive vitamin A. Routine NICU care was given to both the groups.

Retinopathy Of Prematurity Screening: the ROP screening was performed for all the preterm infants included in study by qualified ophthalmologist with expertise in ROP according to the standard guidelines as mentioned above and classified according to the international classification of ROP based on location, extent and severity[13].

- **When to Screen**

First screening is done at 4 weeks of birth. Infants with period of gestation less than 28 weeks (gestation age) or less than 1200 grams birth weight are screened at 2-3 weeks after delivery.

Frequency of Screening:

The follow up intervals was based on the initial ROP findings.

1. **No Signs of ROP:** Follow up examination for infants at risk should be done at 2-3 week intervals until the retina is fully vascularized.
2. **If ROP screening is positive:**

Zone 1:

Stage 1, 2 or 3; ROP without plus disease will be screened weekly because there is a high chance of progression.

Zone 2

- Immature vasculature à once in 2-3 weeks.
- Zone 2 stage 1 ROP à once in 2 weeks.
- Zone 2 stage 2 ROP without plus à once in 1-2 weeks.
- Zone 2 stage 3 ROP without plus à at least weekly.
- In case of pre-plus disease à at an interval of 3-4 day

Monitoring

Babies were monitored for feed intolerance and signs and sympotoms of NEC; stopped vitamin-A supplementation in case of established NEC and with the dose of vitamin-A used in study; no signs of toxicity are seen [11] but for safety purpose infants were monitored for regular clinical assessment of skin for erythema, joints for local swelling, clinical signs of increased intracranial pressure and liver function test(LFT) was done if indicated[11,12].

Sample Size

On the basis of the study conducted by Huiquing sun PhD; Rui cheng PhD, Zhansheg wang MD[10] to detect difference of 35.1% in development of different stages of ROP and severity of ROP between group 1 and group 2 assuming 95% confidence interval with 80% power sample size estimated is 27 in each group . Hence a total of 54 neonates who meet the inclusion criteria of the study were considered as participants for the above study.

Statistical Analysis

The data obtained was coded and entered into Microsoft excel spreadsheet. Categorical data was expressed as rate, ratio and percentage. Continuous data were expressed as mean ± standard deviation and the comparison of the continuous data (mean value) was done by unpaired t test- Mann Whitney U test depending on normality assumptions. The comparison of the categorical data was done by Chi-square test. Chi square test was used to test the significant difference in preterm neonates who develop retinopathy of prematurity. When the expected frequencies were small the cell frequencies were pooled and accordingly fisher's exact test was used. P value < 0.05 was statistically significant.

RESULTS

A prospective interventional study was conducted on neonates born before 34 completed weeks of gestation and admitted to A J Institute of Medical Sciences, Mangalore. The selection of cases was based on the inclusion and exclusion criteria. Out of 54 neonates included in the study, 28 (51.9%) were male and 26 (48.1%) were female. Among them, 12 (22.2%) were classified as very preterm, while 42 (77.8%) were moderate preterm. There was no statistically significant difference observed in the baseline maternal and neonatal characteristics between the two groups.

Out of the 54 neonates enrolled in the study, 27 received Vitamin A supplementation. The mean birth weight of neonates in Group A (without Vitamin A supplementation) and Group B (with Vitamin A supplementation) was 1.69±0.57 kg and 1.63±0.49 kg, respectively. The mean length of neonates in Group A and Group B was 41.8±2.6 cm and 41.56±2.8 cm, respectively. Similarly, the mean head circumference in Group A and Group B was 29.74±2.04 cm and 29.56±1.6 cm, respectively.

A Chi-square test indicated no statistically significant difference in the gender distribution of neonates between the two groups (p>0.05). Among the 54 neonates, there were 12 very preterm neonates (28-31 weeks), equally distributed with 6 in each group, and 42 moderate preterm neonates (32-34 weeks), with 21 in each group.

The maternal characteristics, such as pregnancy-induced hypertension (PIH), preeclampsia, eclampsia, diabetes, and mode of delivery, were found to be comparable between the groups. A Chi-square test showed no statistically significant difference in these maternal characteristics between the groups (p>0.05).

The mean APGAR score in the two groups was 9.07±0.78 and 9.22±0.506, respectively. An unpaired t-test showed no statistically significant difference in APGAR scores between the two groups (p>0.05). The mean duration for the initiation of feeds in the two groups was 3.3±2.1 days and 2.63±2.3 days, respectively. Although neonates who received Vitamin A were started on feeds earlier, an unpaired t-test indicated no statistically significant difference in the duration of initiation of feeds between the two groups (p>0.05).

The comparison of the duration of different modes of respiratory support, including mechanical ventilation (MV), continuous positive airway pressure (CPAP), hood oxygen, and total oxygen supply, was conducted. Using the Mann-Whitney U test, no statistically significant difference was found in the duration of MV, CPAP, hood, or total oxygen supply between the two groups (p>0.05). However, Chi-square tests revealed statistically significant differences in the stage of retinopathy of prematurity (ROP) and the total duration of oxygen supply in both the Vitamin A supplemented group (p<0.05) and the non-supplemented group (p<0.05).

Comparison of Total Duration of O2 Supply with ROP Stages

TOTAL DURATION OF O2 supply			ROP stage				Total	Chi Square test value	P value
			No changes	Stage I	Stage II	Stage III			
Vitamin A not given	<2 days	Count	2	3	2	0	7	6.171#	.013
		%	100.0%	30.0%	16.7%	0.0%	25.9%		
	>=2 days	Count	0	7	10	3	20		
		%	0.0%	70.0%	83.3%	100.0%	74.1%		
Total		Count	2	10	12	3	27		
		%	100.0%	100.0%	100.0%	100.0%	100.0%		
			ROP stage				Total	Chi square test value	P value
			No changes	Stage I	Stage II				
Vitamin A given	<2 days	Count	12	1	0		13	5.787#	.016
		%	63.2%	20.0%	0.0%		48.1%		
	>=2 days	Count	7	4	3		14		
		%	36.8%	80.0%	100.0%		51.9%		
Total		Count	19	5	3		27		
		%	100.0%	100.0%	100.0%		100.0%		

Further analysis using Chi-square tests showed statistically significant differences in the type of ROP and total oxygen supply duration in the Vitamin A supplemented group ($p<0.05$). Fisher's exact test indicated a statistically significant difference in the incidence of ROP plus disease between the two groups ($p<0.05$).

Comparison of Total Duration of O2 Supply with Type of ROP

TOTAL DURATION OF O2 supply			TYPE OF ROP			Total	Chi Square test value	P value
			No ROP	Type 1 (Severe)	Type 2 (Less severe)			
Vitamin A not given	<2 days	Count	2	0	5	7	2.917#	.516
		%	66.7%	0.0%	26.3%	25.9%		
	>=2 days	Count	1	5	14	20		
		%	33.3%	100.0%	73.7%	74.1%		
Total		Count	3	5	19	27		
		%	100.0%	100.0%	100.0%	100.0%		

TOTAL DURATION OF O2			TYPE OF ROP		Total	Chi Square test value	P value
			No ROP	Type 2 (Less severe)			
Vitamin A given	<2 days	Count	11	2	13		
		%	64.7%	20.0%	48.1%	5.040#	.025
	>=2 days	Count	6	8	14		
		%	35.3%	80.0%	51.9%		
Total		Count	17	10	27		
		%	100.0%	100.0%	100.0%		

Comparison of ROP Plus Disease Among Neonates Between The Groups

			Groups		Total	Fishers Exact test	P value
			Vitamin A not given	Vitamin A given			
ROP PLUS DISEASE	No plus disease	Count	21	27	48	2.574#	.023
		%	77.8%	100.0%	88.9%		
	Plus disease	Count	6	0	6		
		%	22.2%	0.0%	11.1%		
Total		Count	27	27	54		
		%	100.0%	100.0%	100.0%		

It was observed that among 20 neonates without ROP, 17 (63%) had received Vitamin A. Among the 29 neonates with Type II ROP, 10 (37%) had received Vitamin A, whereas 19 (70.4%) had not. Additionally, all 5 neonates with Type I ROP had not received Vitamin A. Chi-square test analysis demonstrated a statistically significant difference in the type of ROP between the two groups ($p<0.05$).

Comparison Of The Type Of ROP Among Neonates

			VITAMIN A		Total	Chi square test value	P value
			Vitamin A not given	Vitamin A given			
TYPE OF ROP	No ROP	Count	3	17	20	15.563#	.001
		%	11.1%	63.0%	37.0%		
	Type 1 (Severe)	Count	5	0	5		
		%	18.5%	0.0%	9.3%		
	Type 2 (Less severe)	Count	19	10	29		
		%	70.4%	37.0%	53.7%		
Total		Count	27	27	54		
		%	100.0%	100.0%	100.0%		

Comparison Of The Treatment Required Among Neonates In Two Groups

			Groups		Total	Fishers Exact test value	P value
			Group A	Group B			
Treatment required	No	Count	22	27	49	5.510	0.019
		%	81.5%	100.0%	90.7%		
	Yes	Count	5	0	5		
		%	18.5%	0.0%	9.3%		
Total		Count	27	27	54		
		%	100.0%	100.0%	100.0%		

Regarding the treatment requirements among neonates in the two groups, it was noted that all 5 (18.5%) neonates who required treatment had not received Vitamin A. A Chi-square test confirmed a statistically significant difference in the proportion of neonates requiring treatment between the two groups ($p<0.05$).

DISCUSSION

Retinopathy of prematurity (ROP) is a retinal neovascular disorder and a major cause of visual defects or blindness in preterm infants, even with the current standard of care. Several factors contribute to the development of ROP, which is a vasoproliferative disorder[6]. A definitive preventive therapy is still lacking, and visual improvement after treatment is often poor. The pathogenesis of ROP is associated with the regulation of vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF1)[8]. Inhibition of VEGF during the neovascular phase can prevent destructive neovascularization, thereby reducing the development of ROP. Vitamin A is an important micronutrient for normal visual function. Plasma concentration of retinol is low in preterm infants, reflecting the reduced hepatic stores. Early oral Vitamin A supplementation may protect against ROP[14].

This prospective interventional study investigated the role of early Vitamin A supplementation in ROP outcomes in extremely and early preterm infants. Infants with a gestational age of less than 34 weeks in the study group received Vitamin A supplementation when minimal enteral feeding was started after birth until 28 days of life. In this study, among a total of 54 neonates recruited, 27 neonates were given Vitamin A supplementation (Group A), and 27 neonates did not receive Vitamin A (Group B). Infants received necessary routine care and were screened for ROP, and the results were compared. The baseline characteristics of the neonates were matched, and the incidence of mild and severe ROP development was lower in the Vitamin A-supplemented infants compared to the control group.

The present study was conducted to evaluate the role of Vitamin A supplementation in reducing the incidence and severity of ROP. A comparison between Vitamin A-supplemented and unsupplemented preterm infants showed that the incidence of ROP was higher in the control group, with a significant statistical difference. In the unsupplemented group, retinopathy progressed to severe stages requiring treatment (laser photocoagulation or cryotherapy). These results agreed with Francesca Garofoli et al[11]., who stated that Vitamin A-supplemented infants, compared to unsupplemented very low birth weight (VLBW) preterm infants, showed a higher incidence of ROP in the control group, which was statistically significant considering ROP grade ≥ 2. In the unsupplemented group, retinopathy had progressed to severe stages, definitely requiring therapy.

Our results showed that early Vitamin A supplementation reduced the severity and incidence of ROP, which agreed with Helen Mactier et al[15]., who stated that early high-dose of intramuscular Vitamin A supplementation improved retinal sensitivity at 36 weeks of postmenstrual age (PMA) in preterm infants at risk of ROP. This study highlights the beneficial effects of early Vitamin A supplementation on

the developing retina and lung, suggesting a role for early Vitamin A supplementation in promoting postnatal retinal maturation. In the present study, oral Vitamin A was used instead of the intramuscular preparation due to the ease of administration and less invasiveness, indirectly showing that oral absorption of Vitamin A is satisfactory to raise serum Vitamin A levels. However, the current study did not focus on the role of Vitamin A in the prevention of bronchopulmonary dysplasia (BPD).

Our results indicate that the incidence of any stage of ROP was significantly higher in the control group compared to the Vitamin A-supplemented group ($p = 0.0001$). A significant difference in the development of severe ROP requiring treatment between the Vitamin A-supplemented and control groups was observed ($p = 0.023$), which partially aligns with the results of a systematic review by Yanxiu Ye et al[16]., where the incidence of ROP of any grade was significantly different between the Vitamin A-supplemented and control groups ($p < 0.0001$). However, no significant difference in the incidence of ROP requiring treatment was observed ($p = 0.59$).

Our results show a significant difference in the development of severe ROP (Type 1 ROP) requiring treatment between the Vitamin A-supplemented and control groups ($p = 0.023$), in agreement with Huiqing Sun et al[10]., who stated that the incidence of Type 1 ROP was lower in Vitamin A-supplemented extremely preterm infants ($p = 0.034$). However, in our study, most babies were born at a gestational age of 28-34 weeks (very and moderate preterm), and a few extremely preterm infants who were initially included died of various complications before completing 28 days. The serum Vitamin A levels of the two groups were comparable at baseline, but the serum Vitamin A level in the supplemented group was significantly higher than in the control group. However, in our study, we did not measure Vitamin A levels due to financial and facility constraints.

This study also aimed to find an association between the duration of oxygen therapy and ROP. Our results showed that the duration of oxygen therapy is an important risk factor associated with the development of ROP. A comparison of the incidence of any stage of ROP in babies requiring oxygen therapy for less than 2 days versus more than 2 days in both the control and study groups showed a significant difference ($p = 0.013$, $p = 0.16$). Our results were comparable with Teoh et al[17]., who found an association between the duration of oxygen therapy and ROP ($p = 0.004$). However, they suggested that continuous monitoring of VLBW infants on oxygen therapy is needed and that supplemental oxygen therapy should be terminated as soon as there is no further indication for it.

The strength of our study lies in its prospective interventional design. As there are no standard recommendations for Vitamin A supplementation in preterm neonates as a preventive therapy, although small studies have shown that Vitamin A helps reduce the incidence and severity of ROP, this study was conducted to evaluate the same in our hospital setting, contributing to the existing evidence. Additionally, the role of oxygen duration as a risk factor for ROP was studied since the role of oxygen therapy as an independent risk factor remains controversial.

The limitations of this study include its single-center design and small sample size. Many confounding factors, such as neonatal sepsis, multiple blood transfusions, and prolonged oxygen therapy, may have influenced the results as they also contribute to the severity of ROP. The caretaking nurses and neonatologists were not blinded to specifically monitor for adverse effects of Vitamin A. Serum Vitamin A levels could not be measured due to financial and facility constraints.

CONCLUSIONS

- According to the current study, the incidence of any stage of ROP between Vitamin A-supplemented and unsupplemented preterm neonates was statistically significant ($p = 0.001$), suggesting a preventive role of Vitamin A in ROP.
- Progression of ROP to its severe form requiring treatment was observed more in the unsupplemented preterm neonates compared to Vitamin A-supplemented preterm neonates ($p = 0.019$), indicating a protective role of Vitamin A in preventing the progression to severe ROP.
- Long-term oxygen therapy showed an association with the incidence and severity of ROP in both the Vitamin A-supplemented and unsupplemented groups, with statistical significance.
- Since Vitamin A supplementation as a preventive measure for ROP remains a matter of debate, the outcomes of this study may be important for planning future trials to confirm the usefulness of oral administration in mitigating ROP severity in preterm infants at risk of ROP.

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