http:// jpp.mums.ac.ir
Original Article (Pages: 18902-18911)

The Effect of Oral Vitamin A in the Prevention of Retinopathy of Prematurity in Premature Infants with Low Birth Weight

Maryam Mohammadi [1], Maryam Shokouhi Solgi [2], Nasrin Jiriaee [3], Mohammad Amin Rezaei [4], * Behnaz Basiri [2]

[1] Behavioral Disease Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran.

[2] Neonatal Department, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran.

[3] Department of Social Medicine, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran.

[4] Student Research Committee, Kermanshah University of Medical Sciences, Kermanshah, Iran.

Abstract

Background: Retinopathy of Prematurity (ROP) is one of the most common complications in premature babies, whose severe disease can have a long-term effect on the visual performance of babies. In some studies, it has been shown that the administration of vitamin A may be effective in these infants; however, sufficient studies have not been conducted in this field. This randomized clinical trial aimed at investigating the effect of oral vitamin A in the prevention of ROP among premature infants with low birth weight, admitted to the neonatal intensive care unit of Fatemiyeh Hospital.

Methods: In this clinical trial, 66 premature babies with a gestational age of less than 34 weeks who were admitted to the neonatal intensive care unit due to prematurity and respiratory distress were included. The patients were randomly divided into two groups and one group received 3000 units of oral vitamin A daily for 28 days or until discharge, in addition to the usual daily care. In the control group, only usual care was given. Stages of ROP were evaluated according to the International Classification of Retinopathy of Prematurity (ICROP). The rates of Necrotizing Entero-Colitis (NEC), Broncho-Pulmonary Dysplasia (BPD) and Intraventricular Hemorrhage (IVH) were investigated in both groups.

Results: Both groups had no statistically significant differences in terms of basic variables. No side effects were observed in the intervention group. The rates of Necrotizing Entero-Colitis (NEC), Broncho-Pulmonary Dysplasia (BPD) and Intraventricular Hemorrhage (IVH) were lower in the intervention group, but did not show a statistically significant difference with the control group. The incidence rate of ROP was found to be 43.4% in the intervention group and 59.4% in the control group (P=0.172). Among the 14 infants of the intervention group, where retinopathy of prematurity occurred, 7 patients had grades II and III, while 17 cases (89.5%) of the 19 affected infants had grades II and III in the control group (P=0.019).

Conclusion: Our findings revealed that the administration of oral vitamin A in premature infants with low weight can be an effective therapeutic strategy to reduce the risk of retinopathy.

Key Words: Prematurity, Retinopathy of prematurity, Vitamin A.

* Please cite this article as: Mohammadi M, Shokouhi Solgi M, Jiriaee N, Rezaei MA, Basiri B. The Effect of Oral Vitamin A in the Prevention of Retinopathy of Prematurity in Premature Infants with Low Birth Weight. J Ped Perspect 2024; 12 (07):18902-18911. DOI: **10.22038/ijp.2024.82758.5484**

****Corresponding Author:***

Behnaz Basiri. Neonatal Department, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran. Email: researcher415m@gmail.com

Received date: Sep.22,2024; Accepted date:Oct.27,2024

1- INTRODUCTION

Premature birth accounts for about 10% of all births, and prematurity accounts for about 80-60% of the cause of morbidity and mortality in infants without congenital anomalies worldwide (1). Premature birth represents a significant burden on the health care of any country and is one of the main causes of infant mortality and long-term complications in these infants; therefore, prevention of diseases related to prematurity is considered as a health priority. The number of premature babies who survive is likely to increase in the coming years.

Iran is one of the regions with high prevalence of premature birth; and premature babies comprise approximately 10% of births (2).

Retinopathy of Prematurity (ROP), initially described as retrolental fibroplasia, is a vasoproliferative vitreoretinal disorder in preterm infants in developed and developing countries (1, 2). This disease occurs in preterm infants via incomplete or immature retinal vascularization in preterm infants, which can lead to a wide range of vision disorders from minor correctable visual acuity deficits to retinal detachment, and visual impairment or blindness worldwide(3). Early diagnosis and therapeutic interventions can prevent blindness in many of these infants, severe disease can lead to unfavorable outcomes (i.e., retinal detachment and blindness), if not promptly and adequately diagnosed and treated (4).

Various risk factors are involved in ROP including low gestational age, low birth weight, Intraventricular Haemorrhage (IVH), late onset sepsis, and blood transfusion, as well as oxygen-therapy, and use of indomethacin, surfactant, and erythropoietin.

Although extended oxygen inhalation treatment and changes in oxygen level affect the progression of the disease, the most common cause of ROP is prematurity and Small Gestational Age (SGA). Babies weighing less than 1500 grams and with gestational ages less than 31 weeks are more at risk of retinopathy of prematurity (5, 6). Genetic factors may increase the risk of ROP. Blood transfusion, glucose concentration and infections during infancy can be risk factors for ROP. In developed countries, the probability of blindness caused by ROP is less than 10%, but it reaches 40% in developing countries due to the limitations of retinal examination and follow-up of patients and NICU facilities. For this reason, localization of screening criteria in each country is recommended (7, 8).

Preventive strategies for ROP are still lacking. Prevention of disease can significantly reduce the future damage and complications of this disease. In some studies, conducted in recent years, the possibility of prescribing vitamin A in reducing the incidence of ROP has been raised.

A previous study has reported that intramuscular supplementation with vitamin A can be capable of preventing ROP (9) and another revealed safe correction of vitamin A deficiency in most preterm infants who tolerate feeds via supplementation with 5,000 IU of vitamin A per day (10). Vitamin A supplementation may be able to reduce the incidence of ROP of any grade (11).

However, controlled trials conducted regarding oral vitamin A supplementation are of great importance for prevention of ROP in preterm infants.

Therefore, the present study was conducted to investigate the effect of oral vitamin A consumption in the prevention of ROP in premature babies with low birth weight and if possible to prevent the complications and problems of these patients.

2- MATERIAL AND METHODS

2-1. Design and participants

This clinical trial was conducted on 66 premature babies with a gestational age of less than 34 weeks who were admitted to Fatemiyeh Hospital in the period of 2021-2022 due to prematurity. Sampling in this study was done as consecutive sampling of premature babies weighing less than 1500 grams at the time of birth.

A checklist designed to collect information that includes some demographic information, the type of treatment intervention and the investigated outcomes (incidence and severity of ROP).

2-1-1. Sample size

The sample size was calculated by the formula of comparing two ratios as follows. Considering the test power of 80% and retinopathy prevalence of 19% in the intervention group and 33% in the control group, the sample size was estimated to be 66 cases and 33 cases in each group.

$$N= (z_{1-\alpha/2}+z_{1-\beta})^2 [p_1(1-p_1)+p_2(1-p_2)]\div(p_1-p_2)^2$$

2-1-2. Inclusion and exclusion criteria

Inclusion criteria included: 1. Babies whose birth weight is less than 1500 grams or whose gestational age is less than 34 weeks (premature baby), 2. Babies with birth weight between 2000-1500 grams and unstable conditions admitted to NICU, 3. The parents consented to participate in the study, and 4. Babies not having any underlying disease that would cause problems in the study implementation process. Exclusion criteria included: 1. Babies whose files are incomplete in terms of required information, 2. Babies who died before four weeks. 3. Babies having obvious congenital abnormalities and heart disease.

2-2. Procedure

In the intervention group, 3000 units of oral vitamin A per Kg of infant's weight were prescribed orally from the time of the start of oral feeding. Vitamin A was not prescribed in the control group. The time of the first retinal examination in both groups, in babies with a delivery age of 27 weeks and more, was performed four weeks after birth. The time of the next eye examinations was determined based on the findings of the initial examination. The examination of the infants examined in the present study was done by a retinal fellowship ophthalmologist at the neonatal intensive care unit of Fatemiyeh Hospital and the discharged infants at the eye clinic. The study data included demographic characteristics of the baby, and prenatal records recorded in the medical record. In order to conduct this research, retinopathy records were extracted from the medical records of newborns and discharged babies through correspondence with their parents and finally recorded in the researcher's checklist.

2-3. Stages of the disease

Stages of ROP were evaluated according to the International Classification of Retinopathy of Prematurity (ICROP).

Zone I: a circle in the center of the optic disc whose radius is twice the distance from the fovea to the center of the optic disc.

Zone II: from the edge of Zone I to the point of contact with the ora serrata and around the area near the temporal equator

Zone III: Crescent-shaped area in front of Zone II

Stage 1: Existence of demarcation line

Stage 2: The existence of Ridge along with small tufts of fibrovascular proliferation

Stage 3: Ridge with extraretinal fibrovascular proliferation

Stage 4: Subtotal retinal detachment: A) without fovea involvement; B) with the conflict of A

Stage 5: complete detachment of the retina. Eye examinations based on postmenstrual age. That is, the sum of the gestational age and the age after the birth of the baby and the findings of the previous examinations end when the baby is no longer susceptible to vision-threatening retinopathy.

The examination was terminated in the following cases:

1. Completion of normal retinal vasculature up to the end of zone II, which is usually observed at 40 weeks of postmenstrual age and is often completed by 45 weeks.

2. Observing the cessation and clear regression of retinopathy symptoms, which included the following:

A) Changing the color of the edges from pink to white

b) No increase in the severity of the disease

c) Passage of blood vessels through the demarcation line

d) Starting the process of replacing active lesions with scar tissue

The rates of Necrotizing Entero-Colitis (NEC), Broncho-Pulmonary Dysplasia (BPD) and Intraventricular Hemorrhage (IVH) were investigated in both groups.

2-3. Randomization

The patients were randomly assigned to the intervention and control groups using the randomized block method. For this purpose, blocks of four were prepared, with the name of intervention written on two sheets and the name of comparison on the other two sheets. Sheets were piled up and placed in a container, and one sheet was pulled out for each patient without placement. Then four sheets were returned to the container and this process was repeated until the sample size was reached.

The person evaluating the outcome and the researcher were unaware of the drugs received by the patients until the end of the study; therefore, the study was conducted in a double-blind manner.

2-4. Data analysis

In this study, SPSS version 20 software was used for data analysis. A statistically significant level of less than 5% was considered.

Data description was done using descriptive statistics by expressing mean and standard deviation for quantitative variables, ratio, and percentage for qualitative variables. Mann-Whitney test was used to compare quantitative variables, and chi-square test or Fisher's exact test was used for qualitative variables.

3- RESULTS

In this clinical trial, 66 ROP babies with gestational ages less than or equal to 34 weeks and birth weights less than 1500 grams were randomly included in the study. They were equally allocated in the intervention (vitamin A) and control groups.

On average, the babies of the two groups had a gestational age of 30 weeks. Most of the babies were male and were born by cesarean section. In addition, the average birth weight of both groups was 1350 grams. Both groups had no statistically significant differences in terms of the examined variables. Other information is shown in Table 1.

The average duration of the need to receive oxygen was higher in the control group, but there was no statistically significant difference between the two groups (Fig. 1, Table 2).

A lower frequency of bronchopulmonary dysplasia, intraventricular hemorrhage, and NEC was found in the intervention group, but no statistically significant

difference was found between the two groups (Fig. 1, Table 3).

Babies in the intervention group had a lower frequency of ROP, but no statistically significant difference was found between the groups.

The incidence of higher grades of ROP in the control group was significantly higher than that in the intervention group.

Table-1: Comparison of baseline variables and clinical status between the groups

Variables	control group, n=33	intervention group, n=33	P-value
Gestational age (weeks), SD ± Mean	6/2 ± 0/30	0/2± 2/30	974/*0
Birth weight (grams), SD ± Mean	1/352 ±5/1284	9/373±9/1337	553/0*
First minute Apgar, SD ± Mean	9/1 ± 9/5	2/1 ± 9/5	468/0*
Apgar score, 5 minutes), SD ± Mean	8/0 ± 4/7	0/1 ± 2/7	191/0*
gender (male); frequency (percentage)	18 (5/54)	20 (6/60)	618/0†
perform cesarean section; frequency (percentage)	23 (7/69)	24 (7/69)	786/0†
Beginning of oral feeding (day) SD ± Mean	5/1 ±0/4	1/1 ±0/4	927/0*
Complete tolerance of oral feeding (days), SD ± Mean	2/6 ±5/15	2/5 ±0/14	290/0*

Not: *: Mann-Whitney, †: chi2 or fisher exact

Table-2: Comparison of the average duration of oxygen intake between the groups

Variables	control group, n=33	intervention group, n=33	P(Mann-Whitney)
	Mean ± SD	Mean ± SD	
Number of days requiring supplemental oxygen	2/7 ± 4/18	8/9 ± 4/14	069/0

Table-3: Comparison of qualitative outcomes between the groups

Variable	control group, n=33	intervention group, n=33	P(Fisher's exact)
	Frequency (%)	Frequency (%)	
Bronchopulmonary dysplasia	6 (2/18)	3 (1/9)	475/0
Intraventricular hemorrhage	12 (4/36)	11(3/33)	796/0
NEC	8 (2/24)	5 (1/15)	353/0

Table-4: Comparison of the incidence of retinopathy between the groups

retinopathy	control group, n=33	intervention group, n=33	P(chi2)
	Frequency (%)	Frequency (%)	
no	13 (6/40)	19 (6/57)	172/0
yes	19 (4/59)	14 (4/42)	
total	33 (0/100)	33 (0/100)	

Table-5: Comparison of the retinopathy grades between the groups

grades	control group, n=33	intervention group, n=33	P(Fisher's exact)
	Frequency (%)	Frequency (%)	
1	2 (5/10)	7 (0/50)	019/0
2 and 3	17 (5/89)	7 (0/50)	
total	19 (0/100)	14 (0/100)	

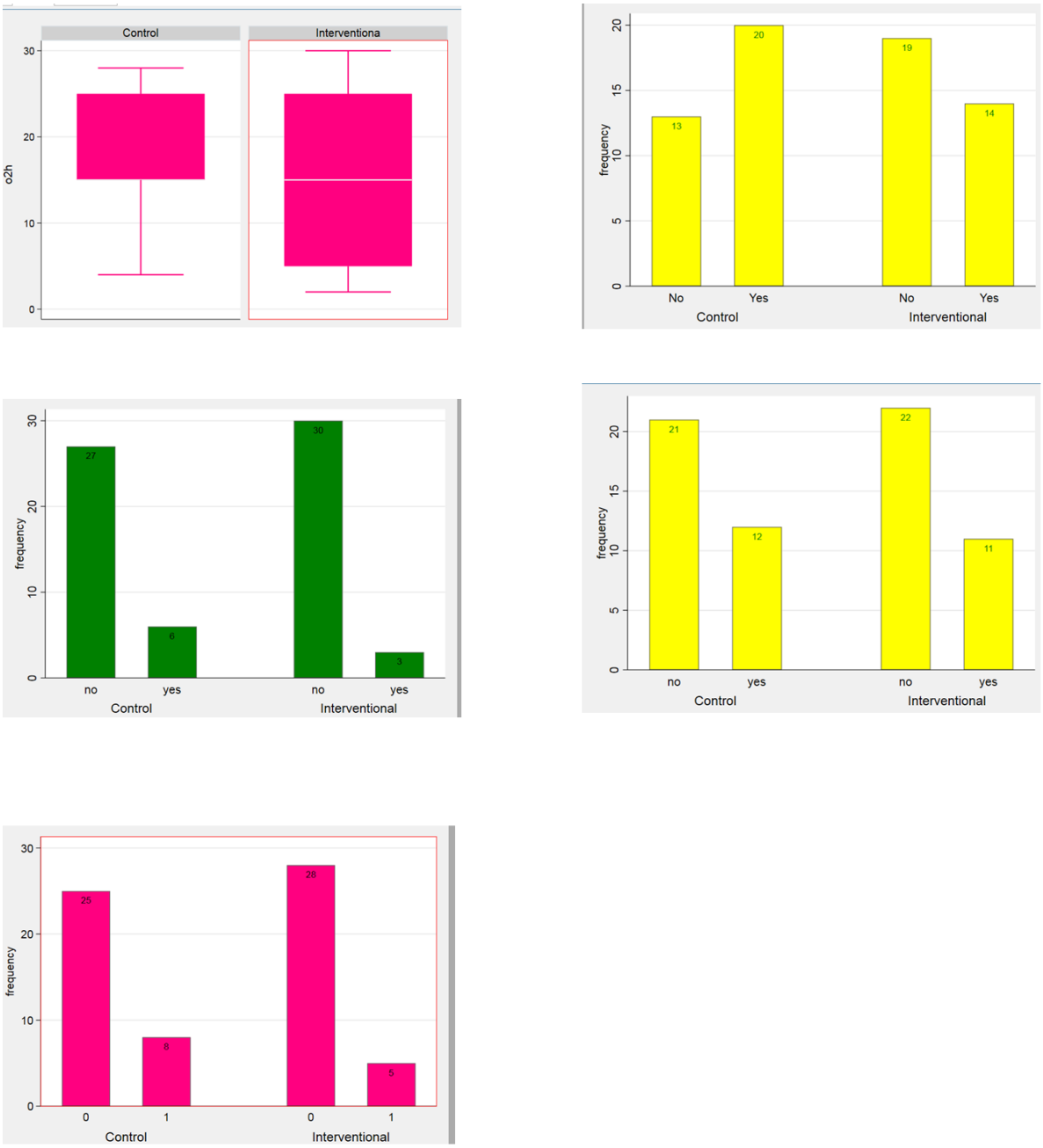

Fig. 1: Box plot diagram of the duration of oxygen intake (a), frequency of retinopathy (b), frequency of BPD (c), frequency of IVH (d), and frequency of NEC (e).

4- DISCUSSION

The current clinical trial was conducted with the aim of investigating the effect of oral vitamin A on preventing retinopathy of prematurity in premature infants with low birth weight.

Currently, two methods have been introduced to treat retinopathy of prematurity, namely laser therapy and VEGF inhibitors, both of which have side effects, requiring alternative treatment methods in some cases (12).Several medicinal methods have been introduced for the treatment of ROP (13–15), one of the suggested medicinal methods is the use of vitamin A supplement. To the best of our knowledge, this is the first study in a country that has examined oral vitamin A supplementation in infants with this prematurity condition. Several methods have been suggested for administration of vitamin A, including intramuscular injection, but this method causes side effects in premature babies due to the need for repeated injections, so the oral administration method was investigated in the present study.

Briefly, the findings of the present study showed that the daily oral administration of vitamin A in the amount of 3000 units can be effective in reducing the severity of ROP. Furthermore, although the incidence of ROP was lower in the intervention group, no statistically significant difference was found between intervention and control groups, which may be affected by the small number of patients examined; however, it can be clinically important.

ROP is a multifactorial disease for which several risk factors are known, including low gestational age, low gestational weight, infection, intraventricular hemorrhage, blood administration, and mechanical ventilation (7, 16, 17). The findings of our studies also confirmed that low gestational age and low birth weight are among the risk factors for the occurrence of this visual system complication.

ROP refers to the abnormal growth of retinal vessels in premature babies, among whom severe disease can lead to vision loss and even blindness if not promptly and adequately diagnosed and treated. Due to the increase in the incidence of prematurity and the probability of survival among these babies, its higher incidence and prevalence can be expected. Therefore, it is important to pay attention to non-invasive methods for its prevention and treatment. Studies that have investigated the effect administration of vitamin A in the occurrence and prevention of ROP have reported conflicting results. Therefore, more studies in this field can be helpful.

A meta-analysis consisting of 67 studies with a population of 21,819 infants demonstrated that oral vitamin A supplementation may be capable of reducing the risk of retinopathy in premature infants, but these findings were obtained from observational studies (18). Garofoli et al. investigated the effect of oral vitamin A supplementation to prevent ROP in 62 premature infants. In the mentioned study, like the present one, 3000 units of vitamin A /kilogram of body weight were given orally in the form of drops. The findings of the aforementioned study revealed that the risk of retinopathy is similar in both groups, but there were 9 cases of ROP grade 1 and no ROP grade 2 in the case group, and 4 cases of ROP grade 1 and 6 cases of ROP with grades higher than 2 were observed in control group ($p = 0.018$), which is consistent with the findings of the present study (4).

Another study with a large sample size was conducted by SUN et al., on 262 infants weighing less than 1,500 grams and less than 32 weeks of gestational age, where 1500 units of oral vitamin A were given to 132 infants from the first day of oral feeding. Their findings showed that

the rate of ROP type 1 in the group receiving vitamin A was significantly lower than that in the opposite group (1.6 vs. 1.9%, P = 0.030). In addition, regression analysis demonstrated a significant relationship between vitamin A serum level and the risk of retinopathy of prematurity type 1 (beta = -2.37) (3).

Another study by Mactier et al. was conducted on 89 babies under 32 weeks weighing less than 1500 grams, where 42 people as the case group received intramuscular vitamin A 10000 units (high dose) three times a week for at least two weeks. The findings of the aforementioned study demonstrated that the retinal sensitivity and functioning were significantly better in the group receiving vitamin A ($p < 0.03$). The reason for the difference between the results of the conducted studies can be due to the vitamin administration method, the selected dose and the characteristics of the selected patients, especially in terms of gestational age and birth weight (19).

Premature babies are very susceptible to vitamin A deficiency because placental transfer from the mother is reduced. Inadequate intake of enteral nutrition for several weeks after birth, poor gastrointestinal absorption, inadequate provision, and unreliable delivery of parenteral vitamin A may exacerbate the issue of vitamin A deficiency. European guidelines on vitamin A supplementation recommend a daily dose of 1000 to 3300 IU/kg body weight in premature infants. On the other hand, vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of ROP. There is evidence that retinoids have a very strong anti-angiogenic activity by inhibiting the expression of VEGF (20). It has been suggested that systemic administration of retinoic acid to very low birth weight infants during oxygen therapy may be a potentially effective therapeutic approach to prevent retinopathy (21).

In the present study, the average number of days receiving oxygen and incidence of bronchopulmonary dysplasia was lower in the intervention group. One of the complications of prematurity, which was almost 2 times lower in the intervention group (9.1% vs. 18.2%) was bronchopulmonary dysplasia; however, the difference was not statistically significant between the two groups, which may be affected by the sample size. Vitamin A is necessary for cell differentiation and surfactant synthesis in the lungs of newborns. The findings of previous studies have also demonstrated that administration of vitamin A was capable of reducing the risk of bronchopulmonary dysplasia (3, 22, 23).

In the current study, we did not observe any serious side effects following the administration of vitamin A in infants. The findings of the studies also show that the administration of vitamin A, especially in oral form, is well tolerated in infants and does not have any specific side effect (3, 4).

4-1. Limitations of the study

This analysis is subject to several limitations. First, due to limited sample size, we could not assess more serious cases to generalize vitamin A effects. Second, not all specimens were measured for vitamin A serum level in the two study groups.

5- CONCLUSION

Retinopathy of prematurity is a sight-threatening complication of prematurity, for which surgical methods are a standard treatment, however, in some cases, medicinal methods are considered. However, limited medicinal methods are available for its prevention and control. Based on the results presented herein, the administration of oral vitamin A in premature babies with low weight can be an effective drug therapy to reduce the risk of severe retinopathy.

6- ETHICAL CONSIDERATIONS

This study was carried out in coordination with the University of Medical Sciences. Informed consent was obtained from the guardians of the patients before participating in the study. And the additional cost was not imposed on the patients. The names of the people remained confidential. The data of the study was collected without including names and individual characteristics and the results were announced in general. The study was registered in the Clinical Trial Center of Iran (ID IRCT20120215009014N403).

6- REFERENCES

1. Fanaroff AA, Martin RJ. Neonatal-perinatal medicine: diseases of the fetus and infant.1987.

2. Reuter S, Moser C, Baack M. Respiratory distress in the newborn. Pediatrics in review. 2014 Oct 1;35(10):417-29.

3. Sun H, Cheng R, Wang Z. Early vitamin A supplementation improves the outcome of retinopathy of prematurity in extremely preterm infants. Retina. 2020 Jun 1;40(6):1176-84.

4. Garofoli F, Barillà D, Angelini M, Mazzucchelli I, De Silvestri A, Guagliano R, et al. Oral vitamin A supplementation for ROP prevention in VLBW preterm infants. Italian Journal of Pediatrics. 2020 Dec;46:1-4.

5. Ugurbas SC, Gulcan H, Canan H, Ankarali H, Torer B, Akova YA. Comparison of UK and US screening criteria for detection of retinopathy of prematurity in a developing nation. Journal of American Association for Pediatric Ophthalmology and Strabismus. 2010 Dec 1;14(6):506-10.

6. Sabri K, Ells AL, Lee EY, Dutta S, Vinekar A. Retinopathy of prematurity: a global perspective and recent developments. Pediatrics. 2022 Aug 1;150(3).

7. Kim SJ, Port AD, Swan R, Campbell JP, Chan RP, Chiang MF. Retinopathy of prematurity: a review of risk factors and their clinical significance. Survey of ophthalmology. 2018 Sep 1;63(5):618-37.

8. Shah PK, Prabhu V, Karandikar SS, Ranjan R, Narendran V, Kalpana N. Retinopathy of prematurity: Past, present and future. World journal of clinical pediatrics. 2016 Feb 2;5(1):35.

9. Shenai JP, Kennedy KA, Chytil F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. The Journal of pediatrics. 1987 Aug 1;111(2):269-77.

10. Landman J, Sive A, Heese HD, Van Der Elst C, Sacks R. Comparison of enteral and intramuscular vitamin A supplementation in preterm infants. Early human development. 1992 Sep 1;30(2):163-70.

11. Ye Y, Yang X, Zhao J, He J, Xu X, Li J, et al. Early vitamin A supplementation for prevention of short-term morbidity and mortality in very-low-birth-weight infants: a systematic review and meta-analysis. Frontiers in Pediatrics. 2022 Apr 7;10:788409.

12. Quinn GE, Dobson V, Davitt BV, Wallace DK, Hardy RJ, Tung B, et al. Progression of myopia and high myopia in the Early Treatment for Retinopathy of Prematurity study: findings at 4 to 6 years of age. Journal of American Association for Pediatric Ophthalmology and Strabismus. 2013 Apr 1;17(2):124-8.

13. González C R, Díaz C M, Garretón C R. Anti-vascular endothelial growth factor (VEGF) drugs compared to laser photocoagulation for treatment of type 1 retinopathy of prematurity. Medwave. 2022 Jan 17;22(01).

14. Filippi L, Dal Monte M. A safety review of drugs used for the treatment of retinopathy of prematurity. Expert Opinion on Drug Safety. 2020 Nov 1;19(11):1409-18.

15. B Beharry KD, Valencia GB, Lazzaro DR, Aranda JV. Pharmacologic interventions for the prevention and treatment of retinopathy of prematurity. InSeminars in perinatology 2016 Apr 1 (Vol. 40, No. 3, pp. 189-202). WB Saunders.

16. Onyango O, Sitati S, Amolo L, Murila F, Wariua S, Nyamu G, et al. Retinopathy of prematurity in Kenya: prevalence and risk factors in a hospital with advanced neonatal care. Pan African Medical Journal. 2018;29(1):1-7.

17. Bahmani T, Karimi A, Rezaei N, Daliri S. Retinopathy prematurity: a systematic review and meta-analysis study based on neonatal and maternal risk factors. The Journal of Maternal-Fetal & Neonatal Medicine. 2022 Dec 12;35(25):8032-50.

18. Fang JL, Sorita A, Carey WA, Colby CE, Murad MH, Alahdab F. Interventions to prevent retinopathy of prematurity: a meta-analysis. Pediatrics. 2016 Apr 1;137(4).

19. Mactier H, McCulloch DL, Hamilton R, Galloway P, Bradnam MS, Young D, et al. Vitamin A supplementation improves retinal function in infants at risk of retinopathy of prematurity. The Journal of pediatrics. 2012 Jun 1;160(6):954-9.

20. Ozkan H, Duman NU, Kumral A, Kasap B, Ozer EA, Lebe B, et al. Inhibition of vascular endothelial growth factor-induced retinal neovascularization by retinoic acid in experimental retinopathy of prematurity. Physiological research. 2006 Jun 1;55(3).

21. Wang L, Shi P, Xu Z, Li J, Xie Y, Mitton K, et al. Up-regulation of VEGF by retinoic acid during hyperoxia prevents retinal neovascularization and retinopathy. Investigative Ophthalmology & Visual Science. 2014 Jul 1;55(7):4276-87.

22. Uberos J, Miras-Baldo M, Jerez-Calero A, Narbona-López E. Effectiveness of vitamin A in the prevention of complications of prematurity. Pediatrics & Neonatology. 2014 Oct 1;55(5):358-62.

23. Darlow BA, Graham PJ, Rojas-Reyes MX. Vitamin A supplementation to prevent mortality and short-and long-term morbidity in very low birth weight infants. Cochrane database of systematic reviews. 2016(8).