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Original Article (Pages: 1919-1925)

# Comparing the Efficacy of High and Low Doses of Vitamin A in Prevention of Bronchopulmonary Dysplasia

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***Abstract***

***Background***

Bronchopulmonary dysplasia (BPD) is one of the most common serious squeal of preterm infants. It involves approximately one quarter of infants with birth weight less than 1500 grams and 30% of less than 1000 grams. Vitamin A has been shown to reduce BPD rate. We compared efficacy of low and high doses of vitamin A for prevention of BPD in very low birth weight preterm infants.

***Materials and Methods***

In a randomized clinical trial, 120 preterm infants with gestation age 32 weeks or less and birth weight less than 1,500 grams were enrolled in the study. Group A (n=60) received 1,500 IU vitamin A intramuscularly three times per week and group B (n=60) received 5,000 IU vitamin A intramuscularly 3 times/week. Vitamin A was continued for 4 weeks in all patients. Oxygen dependency at age 28 days after birth and at 36 weeks' postmenstrual age was determined in all studied infants.

***Results***

The mean gestation age and birth weight in group A was 29.2 ± 2.1 weeks and 1095 ± 211 gr and in group B 28.7 ± 2.1week and 1147 ± 218 grams (P>0.05). Moderate to severe bronchopulmonary dysplasia was detected in 6 (10%) neonates in group A and 13(21.6%) infants in group B, P= 0.09. Mortality rate was 4 (6.6%) infants in group A and 3 (5%) patients in group B (P>0.05).

***Conclusion***

In our study, high and low doses of vitamin A were similar with respect to the BPD, intra-ventricular hemorrhage, and retinopathy of prematurity and total number of days for hospital stay in very low birth weight preterm infants.

***Key Words:*** Bronchopulmonary dysplasia, Preterm infants, Prevention, Vitamin A.

*Please cite this article as: Mahallei M, Mostafa Gharehbaghi M, Majidzadeh L, Hazhir N. Comparing the Efficacy of High and Low Doses of Vitamin A in Prevention of Bronchopulmonary Dysplasia. Int J Pediatr 2016; 4(6): 1919-25.

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Received date Feb13, 2016; Accepted date: Mar 22, 2016

## 1- INTRODUCTION

Bronchopulmonary dysplasia (BPD) is one of the most common and serious sequel of preterm infants. More than 40 years ago, Northway et al. report a case series of 32 preterm infants who developed chronic lung disease with characteristic clinical, radiographic and pathological features following mechanical ventilation for respiratory distress syndrome (1). New BPD is characterized by a histologic pattern consistent with developmental arrest and impaired alveolar development. Alveoli are larger than normal with reduced number but fibrosis, squamous metaplasia and excessive airway masculinization are absent (2). BPD involves approximately one quarter of infants with birth weight less than 1500 g and 30% of less than 1000 g (3). Increased risk of BPD has been reported with patent ductus arteriosus (PDA), pulmonary edema, high fluid intake and duration of oxygen therapy (4-7). One of the current recommendations for BPD prevention is early vitamin A supplementation for very low birth weight infants. Vitamin A is necessary for normal lung development. The biological benefits of vitamin A include improved epithelial integrity and response to infection or injury (8-10). Vitamin A concentration is lower in BPD infants (3, 11) that may result in a reduction of antioxidant protection. Vitamin A deficiency result in necrotizing trachea-bronchitis and squamous metaplasia in respiratory epithelial in animal models and these changes reverse with vitamin A supplementation (12).

Vitamin A supplementation has been identified as a potentially better practice for the prevention of chronic lung disease (13). Nevertheless, studies indicate a need to optimize the duration, route and dose of vitamin A supplementation (14-16). This study was conducted to compare the efficacy of high and low dose vitamin A supplementation to reduce the BPD rate in pre- term infants.

## 2- MATERIALS AND METHODS

This randomized clinical trial was performed at NICU Al-Zahra hospital which is a tertiary referral University hospital in North West of Iran. Pre-term neonates with gestation age less than 32 weeks, birth weight less than 1,500 g were randomly allocated into two groups. Infants with major congenital anomalies, severe birth asphyxia, cyanotic heart disease, intra-ventricular hemorrhage grade III or more at first 3 days of life; congenital pneumonia and meconium aspiration were excluded from the study. Ethic committee of Tabriz University of Medical Sciences approved the study. Written informed consent was obtained from parents. This study was registered in Iranian Registry of clinical trials as IRCT201505253915N17.

A total 120 neonates were included in the study. Infants in group A received intramuscular vitamin A supplementation with dose of 1,500 IU 3 times/week started from the first week of life and continued for 4 weeks (low dose group). Patients in group B (high dose group) were supplemented by intramuscular vitamin A with doses 5,000 IU three times per week for 4 weeks. The primary outcome was the proportion of infants who developed BPD that was defined as continued need to supplemental oxygen at 28 days after birth to maintain oxygen saturation $\geq$ 92%.

The severity of BPD was determined based on the needed Fraction of Inspired Oxygen (FiO2/ PaO2) at 36 weeks' postmenstrual age. We considered BPD as mild, when the infants didn't need oxygen at 32 weeks' postmenstrual age, moderate when needed $Fio_2$ was less than 30% and severe when needed $Fio_2$ was above 30% (6, 12).

Secondary outcome was neonatal morbidity including retinopathy of prematurity, necrotizing enterocolotis, total number of days of mechanical ventilation. Respiratory distress syndrome (RDS) was diagnosed when clinical symptoms of tachypnea (more than 60/min), retractions, expiratory grunting and cyanosis were present in combination with radiological signs of poor lung expansion. Surfactant was given when the infants with RDS need a fraction of oxygen (FiO2) more than 0.4 to maintain oxygen saturation above than 90%. It is routine in our NICU to extubate infants after surfactant replacement therapy and use nasal continuous positive airway pressure (CPAP). Respiratory support management was same in all patients based on routine NICU protocol. Intubation and mechanical ventilation were initiated either when the arterial oxygen saturation were less than 85% or PaO2 ≤ 50 mm Hg while receiving FiO2 ≥ 0.4 or the PCO2 more than 65 mmHg with a PH less than 7.2 on arterial blood gas analysis or there were more than 4 apneic episodes in first hour after extubation or need more than 2 episodes of bagging per hour. All infants had brain sonographic examination at age 3-5 days, 28 days after birth and 36 weeks' post menstrual age by an expert pediatric radiologist. Patent ductus arteriosus (PDA) was diagnosed based on clinical signs and confirmed by echocardiography which was done by pediatric cardiologist. A nurse, who was not involved in the management of patients, completed the questionnaire.

Statistical analyses were performed using the statistical package for social sciences (SPSS) version 16.0. Quantitative data were presented as mean ± standard deviation (SD) and qualitative data as frequency and percent. Independent t test were used for testing continuous scale data and chi square or Fisher exact test for categorical data. A p-value less than 0.05 were considered statistically significant.

## 3- RESULTS

Of 134 infants were eligible in the study, 14 infants were excluded because of death in first 48 hours of life (4 cases), congenital heart disease (3 cases), intraventricular hemorrhage (IVH) grade III or more at first 3 days of life (3 infants), parental refusal (2 patients), neonatal transport to other hospital for surgical reasons ( 2 infants) (**Figure.1**).

A total 120 preterm infants that were enrolled in the study, that 58 (48.3%) were boys and 62(51.7%) were girls. The mean gestation age of studied patients were 28.9±2 weeks and birth weight 1121 ±215g (**Table.1**). There was maternal preeclampsia in 45 patients (37.5%), gestational diabetes in 3 cases (2.5%), and premature rupture of membranes in 31 patients (25.8%).

RDS was diagnosed in 66 (55%) neonates, 33 cases in each group that treated by surfactant replacement therapy, P=0.50. Surfactant was used as single dose in 53 neonates, two doses in 10 patients and 3 infants need 3 doses of surfactant. Mechanical ventilation was used in 9 (15%) neonates in group A and 19 (31.6%) neonates in group B, (P= 0.02).

Respiratory support with CPAP was performed in 55 neonates (91.6%) in group A and 57 (75%) patients in group B (P=0.35) for mean duration of 2.7±1.9 and 3.2±0.4 days respectively. The rate of High flow nasal cannula (HFNC) was at 42 (70%) neonates in group A and 45 (75%) neonates in group B, P=0.34. The mean duration of hospital stay was 50.1 ± 25.1 days in group A and 50.2 ± 23.6 days in group B, p=.97. The mortality rate was 7 (5.8%) which 4 patients (6.6%) in group A and 3 infants (5%) in group B, p=.50. No clinically important evidence of adverse effects of vitamin A was detected.

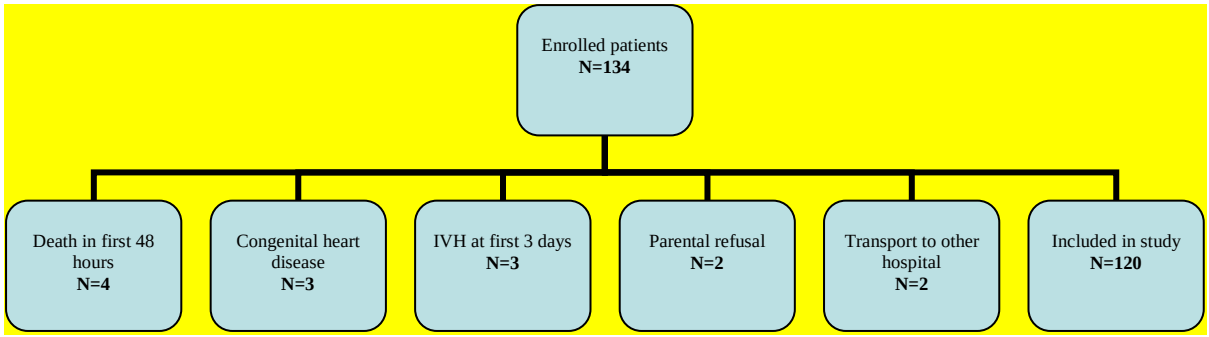


**Fig.1:** Flow diagram for patient enrollment or exclusion in the study

**Table 1**: Demographic characteristics of patients in low and high dose groups

| Variables | Group (low dose) N=60 | Group B(high dose) N=60 | P- value |
|---|---|---|---|
| Gender (n, %) | | | |
| Boys | 28(46.6) | 34(56.6) | 0.18 |
| Girls | 28(46.6) | 34 (56.6) | |
| Birth weight *(g) | 1095±211 | 1147 ±218 | 0.18 |
| Gestation age* (week) | 29.2±2.1 | 28.7±2.1 | 0.25 |
| Apgar score* | | | |
| 1 min | 6.6±0.3 | 6.9±0.2 | 0.29 |
| 5 min | 8.1±0.3 | 8.3±0.2 | 0.31 |

*Mean ± SD

**Table 2**: The frequency of complications of prematurity in studied infants

| Variables | Group A (n, %) | Group B (n, %) | P- value |
|---|---|---|---|
| BPD | | | |
| Mild | 14(23.3) | 14(23.3) | 0.09 |
| Moderate | 4( 6.6) | 8(13.3) | |
| Severe | 2(3.3) | 5(8.3) | |
| IVH | 3(5) | 4(6.6) | 0.50 |
| PDA | 7(11.6) | 12(20) | 0.15 |
| ROP | 4(6.6) | 3(5) | 0.50 |
| Pneumothorax | 0 | 6(10) | 0.01 |

## 4- DISCUSSION

In our study, BPD was diagnosed in 47 (39.2%) neonates that 20 (33.3%) patients were in group A and 27 (45%) patients in group B. BPD was mild in 28 (23.3%) infants, moderate in 12 (10%) and severe in 7 (5.8%)infants. The incidence of BPD is different in various studies that may be due to variation in applied definition, gestation age distribution or other characteristics of studied population and types of applied respiratory support by medical center (17-19).

Regarding to the function of vitamin A in epithelial cell differentiation investigations into the role of high doses of vitamin A in extremely low birth (ELBW) infants for re-epithelialization of lung tissue after acute injury induced by barotrauma or oxygen toxicity to prevent BPD. In one study, 25% of infants, that received vitamin A, were on home oxygen therapy for more than 6 months (12). In our study, oxygen therapy was discontinued before 3 months in all patients.

In a systematic review of five published studies comparing high dose vitamin A to a placebo or no treatment, it is found that high dose vitamin A did not influence rate of death by 1 month of age, but there was a trend to reduction of oxygen toxicity (14, 20-22). Similar to our findings, in a randomized control trial using 5,000 IU vitamin A resulted in reducing duration of intubation, days of oxygen therapy and length of hospital stay in preterm infants who received mechanical ventilation or oxygen supplementation at 24 hours of age (23) . Our study evaluated two regimens for intramuscular administration of vitamin A in very low birth weight infants. Compared with 5,000 IU regimen, administration of lower dose (1,500 IU) was associated with same rate of BPD, intra-ventricular hemorrhage (IVH) and retinopathy of prematurity (ROP); and reduced rate of pneumothorax.

Tyson et al. reported that a dose of 5,000 IU vitamin A given IM three times per week is necessary for normal biochemical concentrations of vitamin A (12). On the other hand Landman et al. studies showed that oral supplementation of 5,000 IU vitamin A daily is as effective as 2,000 IU vitamin A given on alternate days but day have not assess BPD (24). It is recommended not administer high doses of vitamin A during therapy with dexamethasone to avoid exposure of high levels of circulating retinol (25).

In another retrospective cohort study of pre-vitamin A and post vitamin A using in ELBW infants who were routinely cared for with early nasal continuous positive airway pressure (NCPAP), the incidence of moderate to severe BPD decreased from 33% to 22% without significant difference in the number of ventilator days or incidence of intra-ventricular hemorhagea (IVH), necrotizing enterocolitis (NEC) or PDA (26). No clinically important evidence of adverse effects of vitamin A was detected in our study.

### 4-1. Limitations of the study

The major limitation of our study is that serum retinol was not measured in patients. It is recommended future studies with higher number of patients with plasma retinol concentrations measurement.

## 5. CONCLUSION

In our study, high and low dosed of vitamin A were similar with respect to the BPD, intraventricular hemorrhage, retinopathy of prematurity and total number of days for hospital stay in very low birth weight preterm infants.

## 6- CONFLICT OF INTEREST

The authors had not any financial or personal relationships with other people or organizations during the study. So there was no conflict of interests in this article.

## 7- ACKNOWLEDGMENTS

This study was supported by Women's Reproductive Health Research Center. We thank the NICU nurses involved in the care of study infants. We also thank Mrs. Aghebati for her valuable helps.

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