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EFFECTIVENESS OF VITAMIN A IN THE PREVENTION OF COMPLICATIONS OF PREMATURITY : SYSTEMATIC REVIEW

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Abstract

The phrase "vitamin A" refers to a group of chemicals that are fat-soluble and include retinol, retinyl palmitate, and beta-carotene. Vitamin A is a generic name. The numerous metabolites of this compound are required for normal vision, cellular development, epithelial barrier function, and immunological function. In the eyes, periocular glands, respiratory system, gastrointestinal tract, and genitourinary tract, a lack of vitamin A leads to the development of stratified, keratinizing epithelium, which eventually replaces normal epithelium. An excessive amount of vitamin A has immediate as well as long-term negative consequences on one's health. A disorder known as bronchopulmonary dysplasia is something that frequently occurs as a direct result of premature birth. BPD is a disorder that affects around twenty percent of babies who have a very low birth weight and more than fifty percent of infants who have an extremely low birth weight. BPD is a condition that affects approximately twenty percent of newborns who have a very low birth weight. It has the potential to cause a significant amount of morbidity. According to the findings of this research, the impact of vitamin A supplementation on the risk of BPD may be more pronounced in infants who had a lower birth weight than those who had a greater birth weight when compared with the general population. It was associated with a decreased incidence of type 1 retinopathy of prematurity, and it may also have a positive impact on reducing the prevalence of bronchopulmonary dysplasia. It was discovered that supplementing with vitamin A might reduce the severity of VA deficits in extremely preterm babies.

Keyword: *Bronchopulmonary dysplasia; Complications; Prematurity; Vitamin A*

INTRODUCTION

Vitamin A is a general term word for several fat-soluble compounds, including retinol, retinyl palmitate, and beta-carotene. Vision, cellular development, epithelial barrier function, and immunological function rely on its many metabolites. Two types of vitamin A are received from the food. Meat, dairy products, and fish are animal sources of preformed vitamin A (retinol and retinyl ester). Beta-carotenoid (provitamin A) is produced from colored fruits and vegetables. To support biological functions, both ingested forms of vitamin A must be transformed to retinal and retinoic acid after absorption.[1,2]

Vitamin A deficiency causes stratified, keratinizing epithelium to replace normal epithelium in the eyes, periocular glands, respiratory tract, gastrointestinal tract, and genitourinary tract. An excess of vitamin A has both immediate and chronic adverse effects on health.[3] Vitamin A deficiency is significantly more widespread than vitamin A toxicity on a global scale. The World Health Organization (WHO) estimates that 3 million children suffer vitamin A deficiency each year, compared to 200 instances of vitamin A poisoning. Vitamin A deficiency is a significant global public health issue.[4,5]

In nations with a high under-five mortality rate, supplementation is seen as a crucial strategy for significantly decreasing the rates of child morbidity and death owing to avoidable illnesses. It is acknowledged as one of the most cost-effective strategies for boosting childhood survival rates. Vitamin A supplements are used for the treatment of measles, xerophthalmia, and severe malnutrition, as well as for the prevention of vitamin A insufficiency in pregnant women living in locations where vitamin A deficiency is prevalent. The treatment of xerophthalmia is of particular importance since it is one of the few vitamin-deficiency-related disorders that has reached pandemic proportions.[6]

It has been well documented that ocular vitamin A supplementation helps prevent night blindness, a serious concern in underdeveloped nations. Gene regulation is dependent on vitamin A's role in cell morphogenesis, differentiation, and proliferation. In addition, its antioxidant properties reduce free radical damage to DNA.[6,7] It has been shown that vitamin A supplied to ELBW infants during their first weeks of life results in a slight improvement in respiratory outcomes.[8,9] Tyson et al. evaluated a group of 800 very low birth weight (VLBW) children and reported a substantial reduction in oxygen need and BPD of prematurity following the intramuscular (IM) administration of vitamin A during the first weeks of life.[10]

This article aims to look at research studies related to the effectiveness of Vitamin A in the prevention of prematurity complications.

METHODS

Protocol

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines were adhered to in such a way as to ensure that this investigation's methodology was carried out in a manner that was compatible with the suggestions made by those standards. This was accomplished by adhering to the guidelines in such a way that ensured Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020.

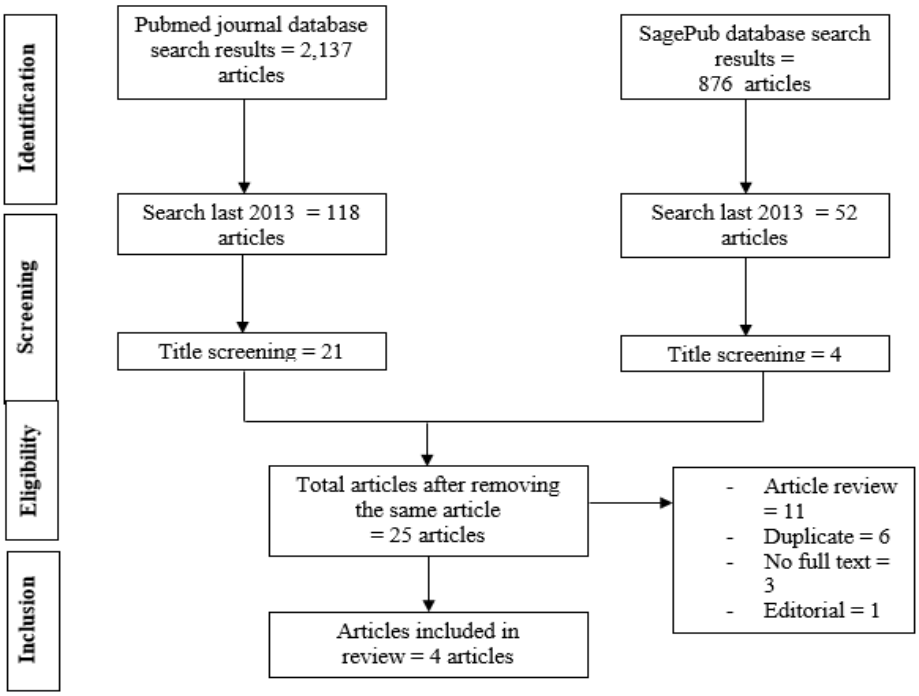

Figure 1. Article search flowchart

Criteria for Eligibility

This literature review seeks to investigate effectiveness of Vitamin A in the prevention of prematurity complications by evaluating or analyzing prior studies on the issue. This is a significant problem raised by the present investigation.

Researchers participate in studies that satisfy the following requirements: 1) To be accepted for publication, publications must be published in English and focus on effectiveness of Vitamin A for prevention of prematurity complications. 2) This assessment included articles published after 2013 but prior to the period covered by this systematic review. Examples include editorials, submissions without a DOI, already published review articles, and entries that are substantially similar to those previously published in a journal.

Search Strategy

The search for studies to be included in the systematic review was carried out from February, 2nd 2023 using the PubMed and SagePub databases by inputting the words: "vitamin A" and "prematurity". Where *("vitamin a"[MeSH Terms] OR "vitamin a"[All Fields]) AND ("premature birth"[MeSH Terms] OR ("premature"[All Fields] AND "birth"[All Fields]) OR "premature birth"[All Fields] OR "premature"[All Fields] OR "prematurely"[All Fields] OR "prematures"[All Fields] OR "prematurities"[All Fields] OR "prematurity"[All Fields])* is used as search keywords.

Data retrieval

Following the completion of a literature review that involved the reading of the titles and abstracts of previously carried out research, the author modified the criteria for what was considered to be included and what was not. In the supplementary materials for this study, the newly defined criteria are broken down and discussed in detail. This brought to light the many dimensions of the problem that call for further investigation, as well as the breadth of the problem itself. After conducting research on a variety of different studies that followed a format that was comparable to this one, the author came to this conclusion. Only papers that satisfied all of the inclusion criteria were taken into consideration while carrying out the procedure of conducting a systematic review. Because of this, the search was limited to locating just material that was pertinent to the inquiry. Research concepts that did not fulfill all of our evaluation criteria were not considered for consideration by our staff. As a consequence of this, it was made certain that a thorough investigation would be carried out.

Because of this work, vital information regarding the research was uncovered, such as their names, authors, publication dates, locations, types of study activities, and parameters. The following is a list of the various product categories that are readily available. These are the kinds of skills that can be picked up via dedicated practice. This information might be provided in a number of different formats, depending on the source from which it was obtained.

Quality Assessment and Data Synthesis

Before deciding which papers to look into further, each author first carried out their own individual analysis of a separate piece of study that was described in the titles and abstracts of the publications. After that, we will read the totality of the publications that meet the inclusion criteria and are therefore suitable for inclusion in the systematic review.

Then, depending on our results, we will decide which papers should be included in the review. The pieces of writing that are going to be looked at have been chosen on the basis of these criteria. in order to make the process of picking articles for the evaluation as straightforward as possible. Which previous studies have been carried out, and what are the characteristics of those studies that make them suitable for inclusion in the review?

RESULT

Uberos, et al (2014)[11] conducted a study with 187 neonates. They did not include in our study 16 children weighing less than 1000 grams and 17 infants weighing between 1000 and 1500 grams because they had either passed away or been transferred to another hospital before we could include them. The vitamin supplement was given to sixty very low birth weight infants. In terms of the length of time spent on oxygen therapy and the likelihood of developing bronchopulmonary dysplasia, we did not find any significant differences between the groups. The infants who were given the vitamin A supplement had up to three times the chance of developing sepsis compared to those who were not.

A study on Thailand showed on day 7 (1.41 ± 0.48 vs. 0.92 ± 0.38 pmol/ L, p <0.001), day 14 (1.48 ± 0.90 vs. 0.96 ± 0.36 micromol/L, p <0.001), and day 28 (1.42 ± 0.63 vs. 0.76 ± 0.30 micromol/L, p <0.001) following vitamin A supplementation, the mean blood vitamin A level was considerably higher in At 28 days, none of the children in the vitamin A supplemented group had vitamin A levels 0.35 micromol/L (indicating severe vitamin A deficiency), compared to 5% of the infants in the control group.[12]

Although not statistically significant, fewer preterm babies in the vitamin A supplemented group required oxygen supplementation at 36 weeks postmenstrual age than in the control group (22.5 vs. 35% relative risk [RR]; 95% CI = 0.40 ± 1.21; p = 0.20). Vitamin A (VA) supplementation was also associated with a significant reduction in the duration of intubation (10.8 ± 3.1 days VA group vs. 26.1 ± 6.4 days control group, p = 0.03), days on oxygen therapy (29.8 ± 5.1 days VA group vs. 58.2 ± 9.1 days control group, p = 0.01), and length of hospital stay (61.9 ± 4.2 days VA group vs. 88.3 ± 7.2 days control group, p = 0.002).[12]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Period	VA Dose	Result
Uberos, 2014[11]	Spain	Retrospective cohort study	187 eligible VLBW infants	January 1, 2008 to December 31, 2012	Vitamin A intramuscularly 5000 IU, three times weekly during the first 28 days of life	16 newborns weighing <1000 g and 17 weighing 1000-1500 g died or were transferred from the 187 eligible VLBW infants. Sixty VLBW newborns received vitamin supplements. Oxygen therapy duration and bronchopulmonary dysplasia risk were similar between groups. Vitamin A supplementation tripled the incidence of sepsis in neonates.
Kiatchoosakun, 2014[12]	Thailand	Randomized control trial	Eighty premature infants weighing <1,500 g who received mechanical ventilation or oxygen supplementation at 24 hours ofage-admitted to Neonatal units	No data	Vitamin A intramuscularly 5000 IU, three times weekly during the first 28 days of life	On day 7 (1.41 ± 0.48 vs. 0.92 ± 0.38 pmol/ L, p <0.001), day 14 (1.48 ± 0.90 vs. 0.96 ± 0.36 micromol/L, p <0.001), and day 28 (1.42 ± 0.63 vs. 0.76 ± 0.30 micromol/L, p <0.001) following vitamin A supplementation, the mean blood vitamin A level was considerably higher in At 28 days, none of the children in the vitamin A supplemented group had vitamin A levels 0.35 micromol/L (indicating severe vitamin A deficiency), compared to 5% of the infants in the control group. Although not statistically significant, fewer preterm babies in the vitamin A supplemented group required oxygen supplementation at 36 weeks postmenstrual age than in the control group (22.5 vs. 35% relative risk [RR]; 95% CI 0.40 ± 1.21; p = 0.20). Vitamin A supplementation was also associated with a significant reduction in the duration of intubation (10.8 ± 3.1 days vitamin A supplemented group vs. 26.1 ± 6.4 days control group, p = 0.03), days on oxygen therapy (29.8 ± 5.1 days vitamin A supplemented group vs. 58.2 ± 9.1 days control group, p = 0.01), and length of hospital stay (61.9 ± 4.2 days vitamin A supplemented group vs. 88.3 ± 7.2 days control group, p = 0.002).
Rakshasbhuvankar, 2021[13]	Australia	Double-blind randomized controlled trial	188 infants	December 2016 and May 2019	Vitamin A intramuscularly 5000 IU, three times weekly during the first 28 days of life	The mean ± SD birth weight (852 ± 201 vs 852 ± 211 g) and gestation (25.8 ± 1.49 vs 26.0 ± 1.39 weeks) were comparable between the vitamin A and placebo groups. There was no difference in the right shift (median [25th–75th percentiles]) of the pulse oximeter saturation versus inspired oxygen pressure curve (in kilopascals) between the vitamin A (11.1 [9.5–13.7]) and placebo groups (10.7 [9.5–13.1]) (P = 0.73). Enteral vitamin A did not affect diagnosis of BPD or other clinical outcomes. Plasma retinol levels were significantly higher in the vitamin A group versus the placebo group on day 28 and at 34 weeks' PMA.
Sun, 2020[14]	China	Double-blind randomized controlled trial	262 extremely preterm infants	August 2015 to December 2017	Vitamin A intramuscularly 1,500 IU, three times weekly during the first 28 days of life	VA-supplemented babies had greater serum VA on Days 14, 28, and postmenstrual 36 weeks than the placebo group (P < 0.001). VA toxicity and intracranial hypertension were absent. VA patients had lower unadjusted rates of Type 1 retinopathy of prematurity (1.6 vs. 6.9%, P = 0.030) and bronchopulmonary dysplasia (18.9 vs 33.8%, P = 0.008) than control patients. Serum VA levels predicted Type 1 retinopathy of prematurity (beta = −2.37) in regression analysis.

Other study showed the mean ± SD birth weight (852 ± 201 vs 852 ± 211 g) and gestation (25.8 ± 1.49 vs 26.0 ± 1.39 weeks) were comparable between the vitamin A and placebo groups. There was no difference in the right shift (median [25th–75th percentiles]) of the pulse oximeter saturation versus inspired oxygen pressure curve (in kilopascals) between the vitamin A (11.1 [9.5–13.7]) and placebo groups (10.7 [9.5–13.1]) (P = 0.73). Enteral vitamin A did not affect diagnosis of BPD or other clinical outcomes. Plasma retinol levels were significantly higher in the vitamin A group versus the placebo group on day 28 and at 34 weeks' PMA.[13]

Other study showed serum VA of the babies who were given VA supplements on Days 14, 28, and postmenstrual 36 weeks was greater than that of the infants who were given a placebo (P 0.001), and there were no side effects seen. There were no reports of any symptoms of VA toxicity or an increase in intracranial pressure. When compared with the control group, the infants in the VA group were less likely to have Type 1 retinopathy of prematurity (1.6 vs. 6.9%, P = 0.030) and bronchopulmonary dysplasia (18.9 vs. 33.8%, P = 0.008). An connection between serum VA levels and the incidence of Type 1 retinopathy of prematurity was discovered through the use of regression analysis (beta = -2.37).[13]

DISCUSSION

A typical consequence of preterm delivery is a condition known as bronchopulmonary dysplasia (BPD). BPD is a condition that affects roughly twenty percent of newborns who have a very low birth weight and more than fifty percent of infants who have an extremely low birth weight (ELBW). It can result in considerable morbidity. The prevalence of BPD has not significantly altered over the past 30 years despite the advancements that have been made in respiratory treatment.[15,16]

Despite the fact that the mortality rate linked with BPD has decreased over the past few years (contributing to just 0.2% of cardiopulmonary-related fatalities for all children 1 year old), BPD continues to be one of the leading causes of death for preterm babies. BPD has also been linked to problems with growth and development, cerebral palsy, an extended stay in the newborn intensive care unit (NICU), and a greater probability of requiring drugs and/or supplementary oxygen after being discharged from the NICU.[16,17]

Retinol, retinal, and retinyl esters are all examples of the class of fat-soluble retinoids known as vitamin A. Retinol is the most common form of vitamin A. After dissolving into micelles in the lumen of the gut, vitamin A, in any of its forms, can then be absorbed by the mucosal cells that line the duodenum.[18] The bulk of the body's vitamin A stocks are converted back to retinyl esters for storage in the liver, although vitamin A may also be stored in the eye and lung tissue. Retinyl esters are transformed first to retinol, then to retinal, and lastly to retinoic acids.[19]

Plasma retinol levels are typically measured to evaluate vitamin A status; however, this practice has some drawbacks. Because hepatic vitamin A stores are depleted before plasma levels are affected, it is possible that marginal vitamin A deficiency will not be apparent based solely on plasma measurements. Although dose-response tests are occasionally used, in clinical practice, simple serum levels are considered to be sufficient for determining whether or not a patient has a significant deficiency. In dose-response tests, small amounts of vitamin A are given to a patient, and changes in serum levels are measured.[18]

Preterm newborns are especially vulnerable to vitamin A deficiency for a variety of reasons. Because maternal vitamin A is largely given to the fetus during the third trimester, hepatic vitamin A reserves are reduced in preterm newborns, as are serum levels of vitamin A and plasma retinol binding protein (responsible for vitamin A transport). It may be difficult to provide sufficient vitamin A to compensate for this loss after delivery. Establishing appropriate enteral feedings in preterm newborns can be challenging. Even in newborns that accept enteral feedings, vitamin A absorption by the young stomach may be inadequate.[19]

Parenteral feeding is typically utilized instead of enteral nourishment, although photodegradation and adsorption to intravenous plastic tubing can cause considerable vitamin A loss. Lipid emulsions can be administered more effectively with vitamin A. Intramuscular (IM) vitamin A treatment improves biochemical vitamin A status and is the preferred method in this group. Although optimal serum vitamin A levels for preterm infants are not known, concentrations < 200 µg/L are generally considered deficient, and levels <100 µg/L suggest severe deficiency.[19]

Intramuscular VA supplementation reduces the occurrence of BPD in extremely low birth weight infants and may reduce the occurrence of ROP. However, because of the pain and danger of injuries associated with frequent intramuscular injections, the practice of intramuscular VA supplementation is not commonly recognized. In preterm newborns, European recommendations on VA supplementation prescribe a daily dosage of 1,000 to 3,300 IU/kg body weight.[9,20,21]
As a result, a median dosage was chosen for this trial to examine the effectiveness and safety of oral early VA supplementation for the prevention of ROP in extremely preterm newborns. The findings of this study back up oral VA supplementation with higher serum VA concentrations in this vulnerable group. In the control group, 30% of newborns had a VA concentration of 0.35 mol/L, indicating that they were VA deficient, compared to 6% in the VA-supplemented group. The VA-supplemented group saw no significant negative effects.[9,20,21]

Other authors suggest that the ratio of retinol to retinol binding protein is a better indicator of vitamin A status in preterm infants, with a ratio of <0.7 considered suboptimal.[19] Vitamin A is involved in the proliferation and maintenance of epithelial cells, including those of the respiratory tract; it is necessary for both cellular differentiation and surfactant production within the lung. Vitamin A deficiency causes necrotizing tracheobronchitis and squamous metaplasia, delayed healing, loss of cilia, increased infection risk, and reduced lung parenchyma alveoli numbers.[22]

Low vitamin A stocks at birth, a predisposition for poor enteral and parenteral intake after birth, and early enteral absorption place ELBWIs at high risk for vitamin A insufficiency. Tyson observed that serum retinol concentration on day 28 was low (<200 g/L) in 73% of ELBWIs who got a sham operation (control group) and that 20% of participants had Vitamin A concentrations of <100 g/L, indicating deficiency. Vitamin A supplementation may be effective for lowering the risk of BPD in ELBWI due to their inherent vitamin A deficiency and decreased absorption efficiency.[23]

In some of the studies, intramuscular injections of vitamin A were replaced with oral vitamin A supplementation since it was considered to be less invasive. Researchers conducted a number of experiments with various supplementation regimens in order to compensate for the immature and unknown enteral ability of the individuals to absorb vitamin A. Wardle measured the amount of vitamin A in the blood 24 hours after the first dose, as well as on days 7 and 28 after administering the medication orally at a dosage of 5,000 IU/kg per day.[23]

The concentration of vitamin A in supplemented newborns was considerably greater within 24 hours after the first dosage (230 g/L versus 150 g/L). At 7 and 28 days of age, the median vitamin A concentration in both groups was greater than 200 g/L. There are currently inadequate data available about oral vitamin A supplementation. Uncertainty exists over the strategies (e.g., timing of consumption and number of daily doses) required to sustain blood vitamin A levels.[23]

According to Landman, et al[24] findings, VAD may be able to be treated with enteral supplementation at a level of 5,000 IU per day in the majority of premature babies who are able to tolerate oral feeding. However, in the research conducted by Sun et al.,[14] ELBW babies were given a lower dose of oral vitamin A, which was set at 1500 international units per day. This resulted in a decrease in both ROP and BPD. In the study that was carried out by Wardle et al., vitamin A was given via enteral administration at a dose of 5000 international units per day for a period of 28 days.

The researchers found that there was no significant difference in the plasma retinol concentrations between the treatment group and the control group at 28 days' PNA. According to Rakshasbhuvankar et al.,[13] these low retinol levels may be the result of poor enteral absorption of the fat-soluble form of vitamin A, whereas the water-soluble form of vitamin A may result in a higher retinol level. This conclusion was reached after the researchers compared the two forms of vitamin A.

However, Sun et al.[14] were able to achieve greater plasma retinol levels in their treatment group despite giving ELBW babies a lower dosage of fat-soluble oral vitamin A. Despite this, the researchers were successful. We are unable to provide an explanation for these disparities in retinol levels or how they may or may not link to the several dosages and dosage forms that were utilized in the trials that were included in our analysis. It is possible that a homogenized worldwide multi-center study will be required in order to define the best dose and effect of vitamin A among very low birth weight infants.

CONCLUSION

According to the findings of this study, the effect of vitamin A supplementation on the risk of BPD may be more prominent in infants who had lower birth weights than those who had higher birth weights. It was related with a lower incidence of Type 1 retinopathy of prematurity, and it may also have a good influence on decreasing bronchopulmonary dysplasia. Vitamin A supplementation was found to minimize VA deficit in extremely preterm newborns.

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