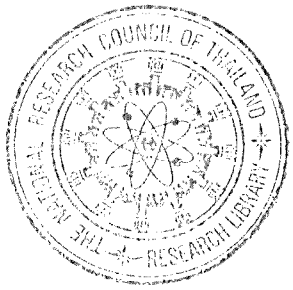

Chapter 2

Literature reviews

Vitamin A Supplementation Reduces BPD

In the late 1980s, Shenai and colleagues at Vanderbilt performed the first trial of vitamin A therapy in infants at risk for BPD.[1] In a placebo-controlled, randomized trial of 40 infants, they found that vitamin A supplementation in the form of retinyl palmitate (2,000 IU intramuscularly every other day for the first 4 weeks of life) reduced the incidence of BPD from 85% to 45%. This study attracted both widespread attention and skepticism, coming shortly after a previously reported beneficial effect of vitamin E supplementation on BPD could not be confirmed in subsequent studies. In addition, there was some skepticism about the magnitude of the beneficial effect in that study. Even at that time, BPD was regarded as a multi-factorial disease whose prevention was likely to require a multifaceted approach; such a remarkable benefit with such a simple intervention was regarded as almost too good to be true. Some of the criticism also stemmed from a misunderstanding of the highly efficient study design employed by the investigators. For example, the incidence of BPD in the control group (85%) was much higher than the incidence at other neonatal intensive care units; the incidence in the retinol-treated group was closer to that reported elsewhere. However, the study was designed intentionally to

enroll only highly selected infants who had the highest risk of surviving with BPD. Therefore, only inborn, uninfected Caucasian infants who weighed less than 1,300 g at birth, required ventilation, and survived for at least 72 hours after birth were enrolled. By enriching the sample with the infants at highest risk for the outcome of interest, investigators showed a significant effect with only 40 patients. However, the highly efficient experimental design raised questions about how well the results could be generalized.

In addition, there was some concern about the hazards of vitamin A supplementation for VLBW infants because average daily doses two to three times higher than recommended were required to normalize plasma vitamin A levels in VLBW infants. Even with the higher daily doses, though, plasma concentrations of retinol and RBP rose and fell during the first 4 weeks of life, suggesting that vitamin A utilization or storage was abnormal in VLBW infants whose developing lungs are recovering from acute lung injury. There are randomized blind placebo controlled trials from Greece, [7,8] they found that vitamin A supplementation 4,000 IU intramuscularly every other day in VLBW infants reduced the incidence of BPD from 31% to 25%.

Some neonatologists expressed a related concern that vitamin A was a drug whose metabolite, retinoic acid, was linked to fetal malformations with first trimester exposure.

However, this concern was not well founded because there should be no risk to the fetus after the sixteenth week of gestation. It is also important to note that the therapeutic goal was only to achieve plasma retinol levels equivalent to those measured in the sera of healthy term infants. Finally, the monitoring of retinol levels was cumbersome, and many neonatal intensive care units did not have access to laboratories that could perform the assay accurately and rapidly.

Vitamin A Supplementation May Not Reduce BPD

Several factors prompted another clinical trial of vitamin A supplementation in 1992. First, the incidence of BPD remained high and perhaps even increased as VLBW infants survival rates increased. The increase in BPD was occurring despite advances in neonatal care, including maternal steroid therapy, surfactant replacement therapy, management of patent ductus arteriosus, high-frequency ventilation, and postnatal steroid therapy. Second, the biologic plausibility and scientific rationale for avoiding vitamin A deficiency in VLBW infants was strengthened further by studies in cell culture systems and in animals.

The investigators from North Carolina and South Africa reported that vitamin A 2,000 IU injection intramuscularly every other day for 28 days did not reduce the incidence of BPD in premature infants.[9, 10] In a three-center study reported by Pearson in

1992[11], 49 infants who weighed less than 1,100 g at birth were enrolled in a randomized, placebo-controlled trial that used the treatment protocol described in the Vanderbilt study. This study population was more representative of the VLBW population in general, and antenatal corticosteroid and surfactant therapies were available. The study found that retinol therapy was safe and reduced the incidence of BPD from 55% to 48%. However, this difference was neither statistically nor clinically significant, and the study was terminated because mathematical projections predicted that a statistically significant difference either would not occur or would require a sample size beyond the capabilities of the three centers involved.

Vitamin A Supplementation Does Not Produce Vitamin A Sufficiency in Many VLBW Infants.

Further studies of vitamin A kinetics in VLBW infants at Vanderbilt documented that enteral supplements of vitamin A could not be substituted for intramuscular injections of retinyl palmitate, probably because of reduced absorption, bioavailability, or both. Because intramuscular injections of vitamin A and plasma monitoring had become a standard of care in the Vanderbilt neonatal intensive care unit (NICU), they also observed that up to 30% of retinol-supplemented infants did not achieve plasma retinol levels in the normal range. Moreover, these infants appeared to be the ones who developed BPD despite

supplementation. Investigators, therefore, developed a more sensitive assay for vitamin A status based on the finding that the normal response to retinol supplementation was a concomitant rise in the plasma RBP level. Infants who eventually developed BPD could not increase their RBP levels in response to retinol supplementation.

These data, combined with findings from the earlier clinical trial, suggested that BPD-prone infants might have some other defect in vitamin A handling that could be overcome only with higher doses. These findings were confirmed in 1996 in a larger pilot study of vitamin A kinetics performed by the NICHD-supported Neonatal Research Network. Results indicated that a higher intramuscular dose of retinol (15,000 IU of retinyl palmitate per week compared with 6,000 to 8,000 IU/wk in the two previous United States studies) was necessary in many infants. Vitamin A intoxication could not be detected either biochemically or clinically at these higher doses.

Vitamin A Found Safe and Effective in Multicenter Trial

In a NICHD-supported trial performed by the Neonatal Research Network[12], more than 800 infants weighing less than 1,000 g at birth were enrolled in a 4-week trial of vitamin A supplementation. A dose of 5,000 IU three times per week was administered intramuscularly for the first 4 weeks of life. Vitamin A supplementation reduced the incidence of BPD at 36 weeks' postconceptional age from 62% to 55% ($P<0.03$, 95%

confidence interval 0.8 to 0.99). There was no evidence of vitamin A intoxication, as assessed by clinical and laboratory monitoring, despite using a higher dose than in previous trials. The total vitamin A intake in the vitamin A supplemented group averaged 3,800 IU/d in contrast to less than 1,000 IU/d in the conventionally supplemented group.

Investigators examined a subset of patients more closely for biochemical evidence of vitamin A sufficiency. They found that 25% to 40% of retinol supplemented infants failed to achieve a normal vitamin A status; 50% to 70% of the placebo-treated group were vitamin A-deficient by biochemical criteria.

Investigators concluded that vitamin A supplementation is safe and reduces the incidence of BPD, although some VLBW infants remain vitamin A deficient despite supplementation at a level three to four fold higher than currently recommended.

It is important to note that a number of VLBW infants in this study were vitamin A sufficient in the absence of any supplementation, suggesting that the regulation of vitamin A stores apparently can be normal in some premature infants. In addition, some of these retinol sufficient infants developed BPD, and retinol-supplemented infants were noted to have abrupt declines in plasma retinol concentrations during episodes of sepsis and airway infection. Obviously, vitamin A is not a cure for BPD, but these findings are likely to prompt further refinements in vitamin A therapy.

Although an 11.2% reduction in the incidence of BPD seems small, several recent multicenter trials for other disorders have prompted national attention despite more modest evidence of efficacy. Another way to estimate efficacy is to estimate the cost-benefit of the intervention. In the NICHD-sponsored trial, the absolute reduction in BPD incidence was 0.07 (0.62 to 0.55). The inverse of 0.07 is 14.3, which is termed by epidemiologists the number needed to treat and represents the number of infants who need to be treated to prevent one case of BPD.

The cost of providing NICU and post-NICU discharge care for an infant who has BPD depends on the severity of the disease. A recent report of the median cost of BPD post-NICU in the United States (not including the incremental costs of the respiratory care of the infant in the NICU) was approximately $19,000, but it could be as high as $450,000. If incremental costs of NICU care of these infants are considered, the cost-benefit ratio is even more favorable. With its record of safety and obvious cost-effectiveness, the routine use of vitamin A in infants at risk for BPD deserves strong consideration.

Beside BPD vitamin A may play the important roles in prevention of oxygen free radicals related complications such as necrotizing enterocolitis (NEC), retinopathy of

prematurity (ROP), respiratory distress syndrome (RDS) and intraventricular hemorrhage (IVH) [13, 14] in premature infants.