**ORIGINAL ARTICLE**

# Comparison of Vitamin A Supplementation versus Placebo in Acute Lower Respiratory Tract Infection

LUBNA RIAZ[1], SOBIA SHAH[2], FOUZIA ISHAQ[3], ASFAND TARIQ[4], AMBREEN ASLAM[5], M. ALAMGIR KHAN[6]
*[1,4]Assitant Professors, Department of Paediatrics, Shaikh Zayed Medical, Complex, Lahore*
*[2]Senior Registrar of Paediatrics, [5]Final Year MBBS Student, Lahore Medical and Dental College, Lahore*
*[3]Associate Profess or Paediatrics, Sir Ganga Ram Hospital, Lahore*
*[6]3rd Year MBBS Student, Shalimar Medical and Dental College, Lahore*
*Correspondence to: Dr. Lubna Riaz, Cell 0332-4396954, E-mail: lubnariaz15@gmail.com*

## ABSTRACT

**Aim:** To compare the efficacy of supplement vitamin A versus placebo in acute lower respiratory tract infection
**Study Design:** Randomized Controlled trial
**Place of Study and Duration**: Paediatrics Unit, Sheikh Zayed Hospital, Lahore and Sir Ganga Ram Hospital Lahore from 1st January 2018 to 31st December 2019
**Methodology:** Two hundred children from 2 months to 5 years with ALRI were included and randomized by lottery method into two groups (100 each) receiving either vitamin A (group A) or placebo (group B). Oxygen, intravenous antibiotics and nebulization were given to patients as per hospital protocol. In group A, vitamin A 1500IU (one drop of vitamin A) while in group B (one drop of olive oil as placebo) was given once daily for 5 days. Patients were re assessed at 5th day of admission for resolution of fever, tachypnea and feeding difficulty and efficacy recorded. The efficacy of vitamin A was compared by using chi square test with $p< 0.05$ as significant result.
**Results:** Patients in group-A (85%) were treated effectively compared to group-B (69%) with statistical significant result (P 0.007).
**Conclusion:** In children efficacy of supplemented vitamin A was significantly higher than placebo with acute lower respiratory infections.
**Keywords: L**ower respiratory infections, vitamin A, Efficacy

## INTRODUCTION

One of the major contribution of morbidity and mortality in under 5 children are ALRTI.[1,2] Approximately 156 million children are estimated to be suffered from pneumonia annually and of these, nearly 1.4 million died.[3,4] A systematic review also reported 1.575 million deaths in children occur due to ARI across the globe.[5,6] In children ALTRI is 52% below two years of age with the common presenting symptoms of fever (90.4%), cough (71.2%) and fast breathing (34.2%). Both viral and bacterial organisms are etiological factor in these infections. Causative of organism of mild to moderate pneumonia are viruses (especially in the first years of life) while bacteria in case of severe pneumonia.[7,8]

Respiratory syncytial virus (RSV) is the main culprit for ARI found in 15-40% children diagnosed as bronchiolitis and pneumonia in developing countries and affect persons of all ages. Almost all children are infected by two years of age, and reinfection is common.[9] Milani et al[10] demonstrated 19.18 % incidence of RSV in children below 5 years in Tehran with almost same clinical manifestations as in other countries (higher prevalence in crowded areas). Globally, RSV is found to cause about 34 million episodes of acute lower respiratory infections in under 5children, leading to almost 3.4 million hospitalization annually.[11] Other viral pathogens include Para influenza, Influenza, Adeno, Human Corona and Bocaviruses[12] and among bacteria, *Haemophilus influenzae* and pneumococci are the important pathogens.[13] Different contributing factors have been consistently responsible for severe acute lower respiratory infections include low birth weight, lack of exclusive breastfeeding, crowding(more than 7 persons/house), exposure to indoor air pollution, incomplete immunization, under nutrition(weight-for-age less than 2 standard deviations) and Human immunodeficiency virus infection are significantly associated with severe ALRI in a consistent manner.[2]

Vitamin A plays an important role in the proliferation, of red cells, lymph cells, antibodies[14] and epithelial integrity. Its well recognized efficacy in measles pneumonia prompt the investigators to explore it further as a possible intervention to hasten recovery and minimize the intensity and duration of ALRTI. Inconsistent results have been reported by different researchers. Some authors suggested no benefits[14,15] while others observed positive effects for population with characteristic demographics such as underweight children or those with pre-existing vitamin A deficiency. Moreover, children with better nutrient or high doses of vitamin A intake have been found to have negative impact with increase frequency of ALRTI.[16,17] In a study by Mahalanabis et al[18] reported that vitamin A treatment did not show any difference in recovery from fever or very ill condition.[18]

Vitamin A supplementation (VAS) doses also influence the outcome. Lower doses have been shown to have decrease risk of respiratory infection while high doses have a negative effect by altering the immune regulatory mechanism that make the child susceptible to more infections.[16] A Cochrane review published in December 2010 on vitamin A supplementation (VAS) for preventing morbidity and mortality in children aged 6 months to 5 years revealed its effectiveness by 24% reduction for all-cause mortality by 24% compared to controls.[19]

In 1986, Sommer and colleagues[20] reported increase death rate in Indonesian children presented with vitamin A deficiency signs (mild xerophthalmia, Bitot's spots, and night

blindness). This finding led to many intervention trials in order to drop mortality and morbidity linked with VAD. So in the light of evidence based research, the World Health Organization (WHO) has long recommended VAS for preschool-aged children (3-4 years old) and mothers within eight weeks of giving birth. Although, Heidarian[21] randomized trial did not favour the vitamin A in managing childhood pneumonia and a 2003 meta-analysis[16] about VAS recommended it should be administered to only those who experienced vitamin A deficiency.

Childhood respiratory infection poses a huge burden on health services due to frequent hospitalization especially in developing countries like Pakistan. Conflicting results have been found among international data regarding the effectiveness of vitamin A for this disease. The rationale of the present study was to delineate the best course of management of acute lower respiratory infections in our population as very few local studies available to see its effect in ALRI in children below 5 years of age.

## MATERIALS AND METHODS

This randomized controlled trial conducted in Paediatrics Unit, Sheikh Zayed Hospital, Lahore and Sir Ganga Ram Hospital Lahore 5th November 2018 to 4th May 2019. Two hundred children were recruited (100 cases in each group) from 2 months to 5 years of both gender with acute lower respiratory infection (ALRI) comprised. It was diagnosed by the presence of clinical features included fast breathing (respiratory rate of more than 50/ minutes, for children aged 2-11 months and more than 40/minutes for children aged 12 months to 5 years according to IMNCI), body temperature of more than 100°C for >24 hours and feeding difficulty (assessed by inability to drink or feed). Those who had history of receiving vitamin A or any sign of vitamin A deficiency (assessed by bitot spots, night blindness and conjunctival or corneal xerosis) were excluded from the study. Children with history of severe bronchial asthma (assessed by tachypnea, bilateral wheeze, hyperinflation on x-ray chest) or congenital heart diseases (assessed by cardiac murmur, tachypnea and ≥3 chest infection in past 6 months, echocardiography) were also removed.

The admitted patients with acute lower respiratory tract infection were randomized by lottery method into two equal groups having either vitamin A (group A) or placebo (group B). Detailed history and clinical examination including respiratory rate, temperature and weight recording followed by investigations i.e. chest X rays, arterial blood gases, complete blood count, C-reactive protein and blood culture in severe ALRTIs. Initially, Oxygen supplementation, intravenous antibiotics and nebulization was given to all patients as per hospital protocol. In group A, vitamin A 1500IU (one drop of vitamin A syrup) was given once a day for 5 days while in group B (one drop placebo in the form of olive oil) was given once daily for 5 days. Patients of both groups were monitored twice daily for temperature, respiratory rate, subcostal or intercostal recession and any feeding problem. Efficacy was measured in terms of clinical discharge at 5th day. Discharge was determined by resolution of all of three including fever, tachypnea and feeding difficulty by 5th day of admission. The type of treatment undertaken in acute lower respiratory tract infection was according to medical ethics, beneficial and non-harmful to the patients. Information was recorded in a predesigned including name, age, sex and address. The data was entered and analyzed through SPSS-22. The Chi square test was applied to compare effectiveness of two groups. Significant P value of < 0.05 was considered.

## RESULTS

Patients distribution according to age showed that 61 (61%) in group A and 55 (55%) in group B were between 2 months-2 years of age while 39 (39%) in group A and 45 (45%) subjects of group B belonged to >2-5 years of age respectively with mean ages were 2.55±1.38 and 2.76±1.42 years respectively. Regarding gender, 46 (46%) in group A and 59 (59%) in group B were male while 54 (54%) in group A and 41 (41%) in group B were females. Comparison of efficacy in both groups showed 85 (85%) in group A while 69 (69%) in group B had resolution of clinical symptoms by 5th day and discharged while 15 (15%) in group A and 31 (31%) in group B were not treated effectively [P<0.05] (Table 1). Stratification for age, gender and BMI were showed in Table 2.

Table 1: Age, gender and efficacy comparison in both groups

| Variable | Group A (n=100) | | Group B (n=100) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Age | | | | |
| 2m - 2 yrs | 61 | 61.0 | 55 | 55.0 |
| >2-5 yrs | 39 | 39.0 | 45 | 45.0 |
| Gender | | | | |
| Male | 46 | 46.0 | 59 | 59.0 |
| Female | 54 | 54.0 | 41 | 41.0 |
| Efficacy | | | | |
| Yes | 85 | 85.0 | 69 | 69.0 |
| No | 15 | 15.0 | 31 | 31.0 |

Table 2: Stratification for efficacy with regard to age, gender and BMI

| Variable | Efficacy | Group A (n=100) | Group B (n=100) | P-Value |
|---|---|---|---|---|
| Age | | | | |
| 2m – 2 yrs | Yes | 52% | 36% | 0.01 |
| | No | 9% | 19% | |
| >2-5 yrs | Yes | 33% | 33% | 0.20 |
| | No | 6% | 12% | |
| Gender | | | | |
| Male | Yes | 37% | 40% | 0.14 |
| | No | 9% | 19% | |
| Female | Yes | 48% | 29% | 0.02 |
| | No | 6% | 12% | |
| Body mass index (kg/m$^2$) | | | | |
| ≥30 | Yes | 32% | 37% | 0.74 |
| | No | 8% | 11% | |
| <30 | Yes | 53% | 32% | 0.000 |
| | No | 7% | 20% | |

## DISCUSSION

Severe forms of respiratory tract infections causing mortality in children <5 years of age.[22] Numerous dietary interventions have been carried out to reduce the frequency of these infections. Supplementation of vitamin A has been observed to play a role in decreasing the severity of symptoms, duration of hospital stay and inhibit further episodes of these infections.

In our study, more than half of participants were around 2 years of age and these children showed significant response (p=0.01) to supplemented vitamin A in comparison to age group >2-5 years. A meta-analysis of 11 randomized clinical trials involving 163567 children on early neonatal vitamin A supplementation (NVAS) showed heterogenous results. NVAS decreased infant mortality in South Asia but in Africa, This decreased mortality in South Asia was seen in context with moderate to severe vitamin A deficiency in mothers and high infant mortality in this region.[23] In contrast, Haider et al[24] did not find any favourable effect of vitamin A administered in neonates at birth in decreasing mortality during the first six months or 12 months of life. Soofi et al[25] observed same results. Although studies from other countries in South Asia (Bangladesh)[26] and India[27] showed its benefit by reducing15% and 10% all- cause mortality respectively. No gender predominance was seen in our study.

85% children with these infections improved in resolution of symptoms in group A (vitamin A supplemented) compared to controls with statistical significant difference (p 0.007). This finding was in agreement with Julien et al[28] study that revealed duration of admission among vitamin A supplemented children with ALRI, the rate of discharge on day 5 as 88.4% in the supplemented group and 73.9% in control group. Similarly, Da Silva et al[29] observed that vitamin A level reduced the duration of pneumonia in children. In contrast, Barreto and others[30] investigated the vitamin A effect on diarrhoea and acute lower-respiratory tract infections in children from North Eastern Brazil and found no beneficial effect.

In lung inflammation, respiratory cells integrity is maintained by immune system which is regulated by vitamin A. Mixed results have been found in different trials with vitamin A supplementation for treatment of diarrhoea and lower respiratory infections. Clinical research has demonstrated that vitamin A supplementation diminishes the intensity of respiratory infections and mortality in children with measles. However, non-measles has its little benefit except those with acute or chronic malnutrition. Children of low middle income countries are often undernourished and vitamin A deficient and exposed to develop frequent infections like acute gastroenteritis or pneumonia that contribute to major chunk of under 5 deaths in low-income countries.

Vitamin A deficiency (VAD) has been the main focus as it is linked with high mortality and morbidity. A 2017 Cochrane review included 47 RCTs from 19 countries (involving 1,223,856 children) on vitamin A supplementation (VAS) for preventing morbidity and mortality in children aged 6 months to 5 years reported that there was 12% decreased risk of all-cause mortality for vitamin A compared with no treatment.[31] This meta-analysis revealed VAS reduced the measles and diarrhoea episodes but had no significant effect on frequency of respiratory disease or hospitalization due to infections. This review concluded that policy of universal supplementation should be maintained for <5 children who are vitamin A deficient.

LMICs have high burden of vitamin A deficiency, affecting 190 million preschool aged children and 19.1 million pregnant females.[32] On the basis of evidence provided by different studies, periodic vitamin A supplementation is recommended by WHO for 6-59 months aged children and to support this national or regional programs have been executed in more than 100 countries across the world. Despite all this, VAD is still prevalent in South Asia and Sub-Saharan Africa[33] and more than one third of children are not getting the life-saving benefit of VAS. The results of this study showed effectiveness of vitamin A in children with lower respiratory infections, so we support WHO recommendation of vitamin A supplementation as this low cost treatment may give benefit to our children by reducing symptoms severity, duration and complications associated with pneumonia/ LRTI. In Pakistan, vitamin A supplementation has already been incorporated as an essential component of Integrated Management of Neonatal and Childhood Illness (IMNCI) strategy to prevent and treat <5 children from diseases in order to improve their survival. Unfortunately, in many areas of the country, it is not being followed so it is imperative to aware our health care professionals to ensure its implementation to get better health outcome in our children.

## CONCLUSION

Effectiveness of treatment with vitamin A supplementation was significantly higher than placebo in infants and young children with acute lower respiratory infections so it can be administered to children with lower respiratory infections along with routine management.

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