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Original research article

ROLE OF VITAMIN C AS AN ADJUVANT THERAPY IN PATIENTS WITH SEVERE PNEUMONIA IN TERMS OF REDUCED HOSPITAL STAY

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Abstract: *Vitamin C is well-known for its antioxidant and immune-boosting properties, which can theoretically influence respiratory infections. Numerous studies have explored the role of vitamin C in preventing and treating respiratory infections such as pneumonia in adults. However, there is limited on its effects as adjuvant treatment in pneumonia, in the pediatric population. We conducted this study to compare the effects of vitamin C vs placebo along with standard therapy, reducing the mean hospital stay duration in children with severe pneumonia.* ***Methods:*** *We conducted a randomized control trial over 1 year (1st September 2023 to 30th August 2024) in Children's Hospital, PIMs. We recruited 120 children aged 2 months to 60 months admitted with severe pneumonia. The patients were divided into two groups GROUP A and GROUP B by randomization using the lottery method. Group A received standard antibiotics plus 200 mg of vitamin C daily and Group B received standard antibiotics with a placebo. Duration of hospital stay, duration of fever, cough duration, days on oxygen, days to improve respiratory distress, and days to improve tachypnea were taken as outcomes* ***Results:*** *This study aimed to assess the clinical efficacy of Vitamin C supplementation in patients' children with severe pneumonia, focusing on its impact on hospital stay duration. Additional outcomes evaluated included the duration of fever, cough, oxygen use, respiratory distress, and tachypnea. The findings from our randomized controlled trial (RCT) revealed no statistically significant differences between the Vitamin C and placebo groups for any of these outcomes. This included hospital stay duration (p = 0.57), fever duration (p = 0.49), cough duration (p = 0.51), days on oxygen (p=0.73), days with respiratory distress (p=0.32), and duration of tachypnea (p-values= 0.93).* ***Conclusion:*** *Although the role of Vitamin C in immune support, its antioxidant activity and anti-inflammatory activity theoretically justify its use in pneumonia, the findings of our study conducted on children did not indicate any significant impact of Vitamin C use on the clinical progression of the disease.*

Keywords: Vitamin C, Severe pneumonia , Pediatric pneumonia, Pneumonia treatment.

Introduction

A country's progress is indirectly related to the health and well-being of its children which is an important public health issue and is measured in form of Under 5 mortality. In 2015 the international community set up a new target in the form of Sustainable Development Goals (SDGs) which aims to reduce under-five mortality to 25 deaths/1,000 live births by the year 2030. (1) As per the demographic survey of Pakistan from 2017-2018 Under-5 mortality has decreased from 112 deaths/1,000 live births in 1990-91 to 74 deaths in 2017-18 approximately a 34% decline. (2)

Pneumonia is a disease of lower respiratory tract that causes inflammation and congestion of the lung parenchyma and in severe cases effects the gaseous exchange at alveolar level. (3) According to WHO pneumonia causes death of 700,000 children under five each year, which is about 2,000 per day. Pneumonia accounts for about 1,400 cases per 100,000 children every year with the greatest incidence reported in countries like South Asia and West and Central Africa. (4) Pneumonia is caused by bacteria, viruses, and fungi. Streptococcus pneumoniae and H-influenza are known to cause most severe forms of pneumonia in children aged between 2 to 5 years. (5) Mortality associated in children with pneumonia in developing countries is attributable to multiple factors such as poverty, malnutrition with deficiency of vitamin A and zinc, poor breastfeeding practices, lack of maternal education, immunizations and proper referral facilities in rural areas. (6)

Vitamin c is an essential micronutrient known to act as a cofactor of enzymes used in biosynthesis of collagen. It aids in absorption of iron and it is an important antioxidant in the body known to strengthen the immune response. (7) Infections lead to production of reactive oxygen species (ROS) from activated phagocytes that help to combat against viruses and bacteria however some of them might harm the host cells contributing to pathogenesis of infection. Vitamin C acts as an antioxidant against these ROS protecting host cells. Phagocytes take up oxidized form of vit c and released reduced form showing that it neutralizes the oxidative stress. (8) Vit C quantity in plasma and leucocyte decrease with the onset of infection and return to normal later on hence affecting vit C metabolism. (9) A study conducted in children aged 5-25 with pneumonia showed significant fall in the levels of vitamin E &vitamin C compared to controls. (10) This evidence shows that vit c could play a role if used prophylactically or therapeutically during an infection to maintain appropriate levels that could neutralize the oxidative stress. Many studies have been conducted to demonstrate the vitamin C role in prevention and treatment of common colds and infections like pneumonia in adults. (11-13) Little work has been done in pediatric population. Given that Pakistan is a developing country with prevailing poverty and malnutrition, the idea for use of a substantially cheap drug like vitamin c, along with the empirical treatment provided for a lethal killer like

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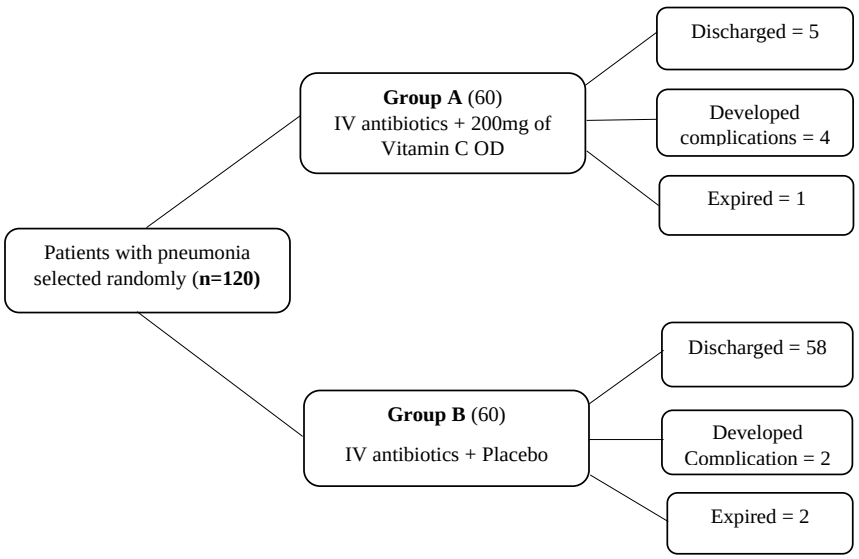

Figure 1: Flow chart showing patients and outcome in both groups

pneumonia is worth exploring. If proven to be significant it can help in decreasing the under 5 mortality in Pakistan.

Methodology

We conducted a randomized controlled trial at PIMs Children's Hospital over a one year period. We included children aged 2 to 60 months who were hospitalized with severe pneumonia, as defined by WHO guidelines. (14) This definition includes presence of cough or difficulty in breathing and tachypnea (> 50 breaths/min for children aged 2–11 months and > 40 breaths/min for children aged 12–59 months), and various danger signs such as vomiting, inability to drink, lethargy, stridor, seizures, unconsciousness, cyanosis, or low oxygen saturation. Children with other infections, severe neutropenia, cardiac, hepatic, renal, or lung conditions, recent multivitamin use, foreign body aspiration, measles, severe malnutrition, or prior treatment were excluded.

By using WHO sample size calculator, sample size calculated was 120 having 60 sample in each group with level of significance 5%, power of test was 90% and population standard deviation 34.83. Test value of population mean was 109.55 and anticipated population mean was 130.64. (15)

120 patients were enrolled using nonprobability consecutive sampling after obtaining parental consent and were randomly assigned via lottery method into two groups: Group A and Group B. Group A received standard antibiotics plus 200 mg of vitamin C daily, while Group B received standard antibiotics and a placebo (water drops with similar taste and color) until discharge or development of complications. First line IV antibiotic used was IV ampicillin while injection ceftriaxone was used as second line.

Clinical improvement was assessed by monitoring fever, respiratory rate, oxygen saturation, oxygen dependency, and length of hospital stay. All the demographic data and outcomes of patients was entered into a preformed performa. Data analysis was performed by SPSS version 26.0. Descriptive statistics (mean ± SD) were analyzed for numerical data (like age, hospital stay), and frequencies and percentages were calculated for categorical data (gender). Chi-square tests were used for categorical comparisons, and independent t-tests were used for numerical comparisons. P-value of less than 0.05 was taken statistically significant.

Results

The baseline characteristics of the two groups (Vitamin C and Placebo) with respect to age, weight, and height are given in Table 1. No significant difference was found between the two groups in terms of age, weight, and height indicated by the P-values of 0.86, 0.9, and 0.06, respectively. This suggests that any differences observed in the outcome between the two groups are likely due to the intervention (Vitamin C or Placebo) and not due to baseline differences.

The baseline categorical characteristics of the two groups (Vitamin C and Placebo) and their respective frequencies and percentages are shown in Table 2. Both groups have a similar distribution of males and females. A slightly higher percentage of children in the Vitamin C group were breastfeeding as compared to the Placebo group. Majority of children in both groups were vaccinated. Most children in both groups received first-line antibiotics and A high percentage of individuals in both groups were discharged. No statistically significant differences were found among the two groups for these baseline categorical variables, as indicated by the P-values (all > 0.05). Both groups had high discharge rates, with minimal complications or mortality and similar treatment protocols for both groups.

Table 3.presents the clinical outcomes of both groups, with specific focus on the duration of hospital stay, duration of fever, duration of cough, duration of oxygen use, respiratory distress, and tachypnea. No statistically significant difference was found between the Vitamin C and Placebo groups (p-values > 0.05) for hospital stay, duration of fever

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and duration of respiratory distress. While the Vitamin C group shows slightly lower means for some outcomes (e.g., cough duration, duration on oxygen, and tachypnea) none of these differences reached statistical significance. This suggests that, Vitamin C did not have a significant effect on the clinical improvement of the patients compared to the placebo group.

Table 1 Baseline Characteristics of both groups

Characteristics	Mean±SD		P-value
	Group 1 (Vitamin C)	Group 2 (Placebo)	
Age (months)	14±13	13±13	0.86
Weight (kg)	8.3±4.2	8.4±4.5	0.9
Height (cm)	69±12	73±12	0.06

Table 2 Comparing categorical variables in both groups

		Group 1 (Vitamin C)		Group 2 (Placebo)		P-value
		Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)	
Gender	Male	29	48	35	58	0.27
	Female	31	52	25	42	
Breastfeeding status	Yes	38	63	32	53	0.26
	No	22	37	28	47	
Vaccinated	Yes	54	90	56	93	0.74
	No	6	10	4	7	
Antibiotics given	First line	45	75	47	78	0.66
	Second line	15	25	13	22	
Clinical Outcome	Discharged	55	92	58	97	0.42
	Developed complications	4	7	2	3	
	Expired	1	1	0	0	

Table 3 Clinical improvement in both groups

Outcomes	Mean ± SD		P-value
	Group 1 (Vitamin C)	Group 2 (Placebo)	
Duration of Hospital stay	4.9 ± 1.2	4.8 ± 1.3	0.57
Duration of fever	3 ± 1.1	2.8 ± 1.1	0.49
Duration of Cough	3.0 ± 1.4	3.2 ± 1.7	0.51
No of days on Oxygen	2.8 ± 1.3	2.9 ± 1.3	0.73
No of days with resp. distress	2.6 ± 0.98	2.4 ± 0.85	0.32
Duration of tachypnea	3.6 ± 1.07	3.7 ± 0.99	0.93

Discussion

The present study aimed to assess the clinical effect of Vitamin C supplementation on patients with pneumonia, specifically examining its effects on the duration of hospital stay. Other parameters like fever duration, cough duration, duration of oxygen use, respiratory distress, and tachypnea were also individually assessed. The results of this randomized controlled trial (RCT) did not demonstrate statistically significant differences between the Vitamin C and the Placebo group for any of the clinical outcomes, including the duration of hospital stay (p-value = 0.57), fever (p-value = 0.49), cough (p-value = 0.51), and other respiratory parameters (all p-values > 0.05).

These findings are in line with some recent meta-analyses and RCTs examining the role of Vitamin C in pneumonia management. While Vitamin C has been suggested to have potential therapeutic effects, particularly due to its anti-inflammatory and immune-boosting properties, the clinical evidence remains mixed.

Several randomized controlled trials (RCTs) worldwide have explored the potential role of Vitamin C in reducing pneumonia severity and duration. For instance, an RCT conducted in India evaluated the effectiveness of Vitamin E and Vitamin C as adjunct therapies in children aged 2 to 35 months having severe lower respiratory tract infections. The results revealed no significant clinical benefit, nor any improvement in oxidative stress or cell-mediated immune response among the treated patients (16). Similarly, a study by Song-I Lee investigated the use of intravenous Vitamin C in adult patients with severe viral pneumonia and respiratory failure. The study found that while intravenous Vitamin C was used as an adjunct treatment, it did not lead to significant improvements in 28-day mortality or other clinical outcomes. Although this study focused on adults and involved intravenous Vitamin C, the lack of statistical significance in terms of mortality supports our findings, where Vitamin C showed no significant effect on hospital stay duration or other clinical parameters. (17)

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The safety and efficacy of vitamin C supplementation in treating pediatric community-acquired pneumonia (CAP) remain under investigation, with current studies primarily focusing on adult populations. The meta-analysis conducted by Sharma et al. suggested potential benefits of vitamin C, indicating a non-significant trend towards reduced mortality and shorter hospital stays in adults with community-acquired pneumonia. (13) Another study done by Hamish, Graham et al was conducted to gather and analyze data regarding additional treatments for children with severe pneumonia in low- and middle-income countries. The authors conclude that while some adjunctive treatments may show promise, particularly high-dose vitamin D in deficient children, the overall evidence does not support the routine use of zinc and vitamin A for improving clinical outcomes in this population. The review also found weak evidence suggesting that vitamin C may reduce the time to symptom resolution in children with severe pneumonia. However, the quality of the studies evaluating vitamin C was considered weak, indicating a need for further research (18) Current literature lacks robust data on pediatric populations, emphasizing the necessity for targeted studies to assess vitamin C's efficacy and safety in children with pneumonia. In Pakistan, where pneumonia remains a major cause of illness and death, particularly among children under 5 years of age, there is growing interest in Vitamin C as a potential supplementary treatment. A study conducted at the Pediatric Department of Islamic International Medical College-Trust, Railway Hospital, in Rawalpindi, involving children 2 months to 5 years of age having severe pneumonia. (19) These children were divided into two groups: one received Vitamin C, and the other received a placebo, similar to our study.

Our study reported mean and standard deviation values for outcomes such as the duration of hospital stay, fever, cough, days on oxygen, respiratory distress, and tachypnea. In contrast, this study focuses on categorical outcomes (i.e., improvement in specific indicators such as respiratory rate, chest indrawing, and oxygen saturation within a set timeframe) with frequencies and percentages, as well as p-values indicating statistical significance. The method for randomization of the study population was not mentioned and the baseline characteristics of both groups were not compared in terms of gender, vaccination status, or breastfeeding status. Statistical tests was also not applied for age and weight distribution in both groups. There was a significant difference between the two groups in terms of number of days needed to show improvement in respiratory rate (3.61 ± 1.50 days for the Vitamin C group vs. 4.04 ± 1.62 days for the placebo group) and oxygen saturation (1.03 ± 0.16 days for the Vitamin C group vs. 1.14 ± 1.0 days for the placebo group). (19) This contrasts with our study, which did not report any statistically significant differences (all p-values > 0.05) for outcomes like hospital stay duration and respiratory measures.

A study carried out at Rawal Institute of Health Sciences in Islamabad showed that length of stay in hospital was significantly reduced in vitamin C as compared with placebo (p-value of 0.001). It did not investigate other clinical outcomes like duration of fever, cough, respiratory rate, respiratory distress and use of oxygen. In this study baseline characteristics of both study groups i.e. weight, height, malnutrition status, breastfeeding and vaccination status were not accounted for. (15)

Aga Khan University performed a meta-analysis that examined the use of vitamin C as an adjuvant therapy which included 4 studies on pneumonia patients. (9) Supplementation doses were different, for example 125 mg/day given until discharge, 200 mg for 4 weeks, and 200 mg till discharge of patient. In the systematic review, one study reported in the vitamin C group, the illness duration reduced to be 3.4 days whereas in the control group, it took 4.5 days. Another research noted that the vitamin C group took fewer days to get improved in oxygen saturation and respiratory rate. Evidence quality for vitamin C's effect on mortality due to pneumonia was also very low, where only one study reporting RR0.21 (95% CI 0.03 to 1.66) from 57 participants. The duration of their hospital stay was noted to be significantly shorter compared to the control group. One study had noted duration of hospital stay to be 6.75 days in vitamin C group and 7.75 in control group. In summary, the overall quality of evidence for the included studies was very low, with considerable uncertainty related to the effectiveness of supplementation with vitamin C in the treatment of pneumonia. The authors concluded that further studies having higher quality are needed to clearly establish the role of vitamin C in this context. (9)

While theoretically supporting its use in pneumonia, taking into account its role in preserving immunity, antioxidant protection, and anti-inflammatory properties, our data suggest that supplementation with Vitamin C may not significantly affect the clinical course of the disease. (20) To our knowledge, there are several reasons for this like degree of Illness, dosage of vitamin C, treatment period and studies having low evidence. Most of the studies, involved patients who had inpatient hospitalizations due to moderate to severe pneumonia. It has been established that Vitamin C can be more efficacious in the prevention of the disease or on the milder form of disease when taken early instead of as an adjunct at the very end, as in the case of severe ones that needed hospitalization.

The lack of consistency in the findings may also be due to variability in the dosing regimen and treatment period used in different studies on Vitamin C. In some studies, Vitamin C doses may be high, while in others it may be in more modest dosage, which affects the outcome obtained. The evidence of the studies conducted so far is very low to prove role of Vitamin C as adjunct in management pneumonia.

Conclusion

In conclusion, although there are some biological justifications for the use of Vitamin C in respiratory infections such as pneumonia, our study, combined with previous global and local RCTs, indicates that Vitamin C supplementation does not improve hospital stay duration and fever resolution and other indices of respiratory parameters. Our study also aligns with more general literature, including meta-analyses, indicating that Vitamin C has very minimal clinical benefits in the management of pneumonia. Therefore, the current evidence does not support recommendations to make Vitamin C a primary therapeutic intervention, and larger sample sizes, diverse dosing regimens, and inclusion of other confounding factors may aid better clarification of a possible role for Vitamin C in the management of pneumonia.

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Declarations

Data Availability statement
All data generated or analysed during the study are included in the manuscript.
Ethics approval and consent to participate.
Approved by the department concerned. (IRB-F1-1/2015/ERB/SZABMU/967)
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The authors declared an absence of conflict of interest.

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Concept & Design of Study

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