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Investigating The Effect of Prescribing Vitamin C on Improving the Clinical Symptoms of Asthma in 2-12-Year-Old Children Hospitalized in the Pediatric Ward of Ghaem and Dr. Sheikh Hospitals, Mashhad, Iran

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Abstract

Background: Asthma is the most common chronic airway disease in children. We aimed to investigate the effect of vitamin C supplementation on improving the asthma symptoms in children.

Materials and Methods: In a double-blind clinical trial: sixty 2-12-year-old children hospitalized with the diagnosis of asthma attack in the Ghaem and Dr. Sheikh hospitals, Mashhad, Iran were randomly assigned into two groups: intervention (receiving vitamin C tablets 500 mg every 12 hours, n=29), and control (receiving placebo, n=31). In each group, at the beginning and end of the hospitalization, one blood sample (3ml) was taken to evaluate the serum level of vitamin C and for other necessary tests. A pediatric resident recorded clinical symptoms at the beginning and every 6 hours until discharged including tachypnea, wheezing, retraction, and hypoxia every six hours until discharge from the hospital. Eventually, the data in the two groups were compared.

Results: The mean age of the hospitalized patients was 33±24 months. There was a significant difference between the intervention and control groups regarding the serum level of vitamin C at the beginning of hospitalization and at the time of discharge. A significant difference was found in tachypnea of the hospitalized patients of both groups at 24, and 36 hours post hospitalization. Existence of wheezing in the patients of the intervention and control groups had a significant difference at 18, 36, and 66 hours post-hospitalization ($p<0.05$).

Conclusion

According to the results, oral vitamin C prescription in patients with acute asthma symptoms leads to improved respiratory status (tachypnea and wheezing) in 2-12-year-old children. Also, it is effective in reducing the duration of hospitalization of these children.

Key Words: Asthma, Children, Vitamin C.

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1- INTRODUCTION

Asthma is the most common chronic disease in children (1). More than 300 million people worldwide suffer from asthma. It is predicted that by 2025, this figure would reach 400 million people. Half of cases with asthma are children younger than 10 while the rest are adults above 40 (2). The prevalence of this disease is increasing in all societies' especially in developing countries and in children, which can be due to increased urbanization and its resulting changes (3). According to the statistics, the prevalence of this disease is 3-35% worldwide (4). The prevalence of asthma in Iran is 2.7-34.4% and the mean prevalence of asthma symptoms throughout the entire country has been reported to be 13.14% (5-7). Asthma is one of the main reasons of referral of children to emergencies and hospitalization (8). Indeed, it is regarded as the third cause of hospitalization in hospitals and healthcare centers among children (9). Developing asthma during childhood can affect the current activities and relations of children and can also potentially influence their future life (10).

The physical effects of asthma including dyspnea for a chronic time reduces energy and vitality (11). Asthma is a multifactorial disease affected by genetic and environmental factors. Around 90% of cases of this disease occur during childhood, suggesting both internal and external risk factors of asthma during childhood. The environmental or external factors include the allergens inside and outside the house, occupational sensitizers, passive smoking, and respiratory tract infections (3, 12). Some studies have shown that change in the diet is one of several factors involved in the development of asthma. Over the last two decades, evidence has increasingly suggested a relationship between diet and asthma (13, 14). According to recent research, adhering to a healthy diet including adequate and balanced consumption of fruits and vegetables, fish and marine food, and different types of plant oils is effective in improving the pulmonary function and quality of life of asthma patients (15). Fruits and vegetables are rich sources of antioxidants including vitamin C and carotenoids, and have been reported effective in preventing tissue oxidative stress and mitigating inflammation of airway tract (16). Some suggestions on the positive effect of vitamin C against asthma date back to the 1940s (17, 18). Some studies have indicated that in patients with asthma, the diets used often lack antioxidants and especially vitamin C (19-23). The results of a study in Egypt indicated that the effect of vitamin C on asthma among children at different ages, exposure to humidity, and severity of asthma are different (24).

The results of a study in Nigeria showed that asthma attacks were reported to be 78% less among those who had consumed vitamin C (25). In contrast, another study in England showed that vitamin C had no effect on asthma or its symptoms (26). Other studies have also emphasized a relationship between vitamin C consumption and asthma (23, 27-32). Thus, since asthma is a common disease among children affected by environmental and genetic factors, and given the contradictory results regarding the role of vitamin C in improving the clinical symptoms of asthma, the aim of this study is to examine the effect of prescribing vitamin C in improving the clinical symptoms of asthma among 2-12-year-old children.

2- MATERIALS AND METHODS

This double-blind clinical trial study was performed on 2-12-year-old children with the diagnosis of asthma attack who had been hospitalized in the pediatric ward of Ghaem and Dr. Sheikh hospitals in Mashhad. All patients with the diagnosis

of asthma who had been hospitalized in the pediatric ward of these hospitals over the last 12 months, and met the inclusion criteria were enrolled in the study. The sample size required with the confidence interval of 95% and test power of 90%, considering d=1, was calculated as 21 in every group. Taking the attrition probability of 50% for greater confidence, it was calculated as 30 in each group and 60 in total (33).

2-1. The inclusion criteria

Children at the beginning of age 2 until the end of age 12 years, with the diagnosis of asthma attack based on history and clinical examination, and if required chest x-ray, hospitalized in the pediatric ward.

2-2. Exclusion criteria

Acute bronchiolitis, pneumonia, congenital heart diseases, severe malnutrition, history of taking vitamin C supplement over the past two weeks, and cystic fibrosis.

2-3. Intervention

Every 2-12-year-old child with a diagnosis of asthma was enrolled in the study by a pediatric resident according to history, as well as clinical and radiological evidence, and randomly assigned into two groups: intervention (n=29), and control (n=31). After patient selection of both groups, the clinical symptoms of patients including coughing, tachypnea, intercostal retraction, wheezing, and hypoxia were recorded by the pediatric resident every six hours until discharge for both groups. This research was conducted as double-blind clinical trial, and only the physician was aware of the contents of both drugs. The control group received placebo (similar to vitamin C tablets in terms of color, taste, and appearance, made by Farabi Pharmaceutical Company). On the other hand, the intervention group received vitamin C tablets (Farabi Pharmaceutical Company), 500 mg every 12 hours (during the hospitalization and at most five days). The rest of the standard and conventional treatments of pediatric asthma were performed according to the typical protocol in the pediatric ward of Ghaem and Dr. Sheikh hospitals for both groups similarly. In every group, at the beginning and end of hospitalization, one 3 ml blood sample was taken from the brachial vein by a skilled nurse in order to evaluate the serum level of vitamin C and for other required tests, and eventually sent to laboratory. In the laboratory, the serum level of ascorbic acid was measured using ascorbate oxidase test using Roche Hitachi 911 analyzer. At the end of this research, the list of patients and serum level of ascorbic acid at baseline and time of discharge were received as a file from the mentioned laboratory and were statistically analyzed.

2-4. Ethical considerations

This study has the permission issued by Ethics Committee of Mashhad University of Medical Sciences (ID-number: 920339). The sampling and procedure of study were performed after acquiring written informed consent form from the parents of the patients participating in this study as well as consent of children above the age of eight. Note that prescription of vitamin C tablet with this dosage, even if the patient has no deficiency, does not cause side effects. Any patient who was intolerant to oral vitamin C or who did not wish to continue, would be excluded. The drug and placebo were provided to the patients freely, and no money was received for conducting the tests twice for every subject.

2-5. Data analysis

After coding, the data were analyzed by IBM SPSS software version 22.0. For description, proper central and distribution indices as well as tables and suitable diagrams were used. For analyzing and comparing quantitative and normal variables, t-test was used, while for

quantitative and abnormal variables Mann-Whitney test was employed. For the qualitative and ranked variables, Mann-Whitney test, while for qualitative and nominal variables, Chi-square test were applied. Data normality was examined using Kolmogorov-Smirnov test. P<0.05 was considered statistically significant.

3- RESULTS

In this study, overall 60 hospitalized patients with the diagnosis of asthma attack were investigated in intervention (n=29), and control (n=31) groups. Out of 60 patients studied, 24 were male (40%) and 36 (60%) were female. In the intervention group 18 girls (62.1%), and in the control group 18 (58.1%) girls were randomly assigned (p=0.244). The mean age of the hospitalized patients was 33±24 months, with the minimum of 12 months and 15 days and maximum of 120 months. The mean age of hospitalization in the intervention group was 27.96±12.6 months, while in the control group it was 38.2±31.1 months (p=0.06). The mean duration of 95% CI: 0.014-0.022, p=0.018 was 44.4±17 hours. In the intervention group, the mean duration of hospitalization was 3983±14.9 hours, while in the control group it was 48.58±18.1 hours. The minimum duration of hospitalization was 12 h (one patient, 1.7%), while the maximum duration of 95% CI: 0.014-0.022, p=0.018 was 78 hours (3 patients, 5%) (p=0.036).

3-1. Level of vitamin C

The vitamin C level was calculated at the beginning of hospitalization and at the time of discharge. The mean serum level of vitamin C in the intervention group (receiving vitamin C) at the beginning of 95% CI: 0.014-0.022, p=0.018was 0.12±0.034 mg/dl, while at the end of 95% CI: 0.014-0.022, p=0.018 it was 3.26±0.66 mg/dl (p<0.017). On the other hand, in the control group, the values were 0.13±0.04 (beginning), and 0.26±0.69 mg/dl (discharge), respectively. According to Mann-Whitney test, a significant difference existed between the two groups (P<0.001, 95% CI: 0.34-2.64).

3-2. Comparison of tachypnea

Tachypnea was recorded in all patients studied in both intervention and control groups at the beginning of 95% CI: 0.014-0.022, p=0.018 and every 6 hours until discharge. According to t-test, in the hospitalized patients of both groups, at 24 hours (95% CI: 0.049-0.51, p=0.019), and 36 hours (95% CI: 0.019-0.60, p=0.036) post-95% CI: 0.014-0.022, p=0.018, a significant difference was observed, while at other times, no significant difference was found (**Table. 1**).

Table-1: Comparison of tachypnea in the intervention and control groups by sex and time of respiratory calculation.

Time of respiratory calculation Tachypnea	Intervention group		Control group		P-value (t-test)
	Yes Number (%)	No Number (%)	Yes Number (%)	No Number (%)	
6 hours after hospitalization	29 (100)	0	31 (100)	0	--
12 hours after hospitalization	25(86.2)	4(13.8)	29(93.5)	2(6.5)	0.304
18 hours after hospitalization	21(72.4)	8(27.6)	27(90.2)	3(10)	0.08
24 hours after hospitalization	16(55.2)	13(44.8)	25(83.3)	5(16.7)	0.019
30 hours after hospitalization	8(42.1)	11(57.9)	17(65.4)	9(34.6)	0.121
36 hours after hospitalization	5(26.3)	14(73.7)	15(57.7)	11(42.3)	0.036
48 hours after hospitalization	2(18.2)	9(81.8)	8(38.1)	13(61.9)	0.248
54 hours after hospitalization	1(33.3)	2(66.7)	7(77.8)	2(22.2)	0.236
60 hours after hospitalization	1(33.3)	2(66.7)	1(11.1)	8(88.9)	0.455
72 hours after hospitalization	0	3(100)	0	9(100)	--

3-3. Comparison of the severity of wheezing

The severity of wheezing was calculated and recorded at the beginning of hospitalization and every 6 hours thereafter for both intervention and control groups. Wheezing was examined through lung auscultation of the patients. According to **Table.2**, there was a significant difference between the two groups in terms of wheezing at hours 18, 36, and 66 post-hospitalization: (95% CI: 0.028-0.035, p=0.034), (95% CI: 0.041-0.049, p=0.045), and (95% CI: 0.014-0.022, p=0.018). The peripheral blood O_2 saturation at the beginning of hospitalization and every six hours thereafter until discharge was measured using pulse oximetry device and recorded. No significant difference was observed between the two groups according to Mann-Whitney test regarding O2sat. Presence and absence of coughs among the study patients was captured from the very beginning of hospitalization, and continued every six hours until discharge. No significant difference existed between the two groups according to Fisher exact test and Chi-square test regarding the presence or absence of coughs. In all of the study patients of both control and intervention groups, from the beginning of hospitalization and every six hours thereafter until complete remission, presence or absence of intercostal or subcostal retraction was recorded. According to Fisher exact and Chi-square tests, no significant difference was observed between the two groups regarding presence or absence of retraction at different times of calculating retraction.

Table-2: Comparison of the presence of wheezing in patients in the intervention and control groups by wheezing calculation time.

Wheezing calculation time	Intervention group		Control group		P-value
	Yes Number (%)	No Number (%)	Yes Number (%)	No Number (%)	
12 hours after hospitalization	28 (96.5)	1 (3.5)	31 (100)	0	0.768
18 hours after hospitalization	22 (75.8)	7 (24.2)	27 (87)	3 (9.6)	0.034
24 hours after hospitalization	19 (65.5)	10 (34.5)	26 (83.8)	4 (12.9)	0.148
36 hours after hospitalization	15 (51.7)	4 (13.7)	20 (64.5)	6 (19.03)	0.045
48 hours after hospitalization	5 (17.2)	6 (20.6)	10 (32.2)	11 (35.4)	0.563
66 hours after hospitalization	0	3 (10.3)	7 (24.1)	2 (6.4)	0.018
72 hours after hospitalization	0	3 (10.3)	2 (6.4)	7 (22.5)	0.545

4- DISCUSSION

The aim of this study was to examine the effect of prescribing vitamin C in improving the asthma symptoms in 2-12-year-old children. The results indicated that vitamin C consumption was effective in reducing the hospitalization period and improving respiratory distress including tachypnea and wheezing among these children. Asthma is one of the most common chronic diseases of children. This disease develops at any age, though most cases of incidence are observed in young individuals. Although it is said that asthma is incurable, in most cases it is controllable (1, 2). The prevalence of this disease is growing in all societies' especially in developing countries and among children, which can be due to increased urbanization and its resulting changes (3). Airway tract inflammation is the most common manifestation in all patients with asthma.

This inflammation develops through sensitivity, viral respiratory infections, and the stimulants that exist in the air. Pediatric asthma is a disorder which is implicated by genetic and sensitivity factors. Around 75 to 80% of cases have significant degrees of various types of sensitivity (3, 12-16). Airway tract inflammation leads to their stimulation and increased response. In addition, long-term inflammation of the airway tract can cause damage to this tract. A point of interest has always been the effect of nutritional supplements especially vitamins on the severity or frequency of asthma symptoms (22). Regarding the relationship between the effects of vitamin C on asthma, various studies have been performed, which have found discrepant results. Some have shown that in patients with asthma, the diets used seldom contain antioxidants and especially vitamin C (19-23). The results of a study in Nigeria showed that asthma attacks were reported to be 78% less in those who had consumed vitamin C (25). Other studies have also emphasized a relationship between vitamin C consumption and asthma (23, 27-32).

The results of a study in Egypt showed that the effect of vitamin C on children differs considering age, exposure to humidity, and severity of asthma (24). In contrast, a study in England showed that vitamin C had no effect on asthma or its symptoms (26). In the study by Kordansky et al., the effect of vitamin C was examined on improving the symptoms of asthmatic patients through measuring FEV1. According to this research, no relationship was found between this vitamin and improving asthma symptoms (34). According to previous studies, the fundamental role of free oxygen radicals, which are released from macrophages of alveolar wall, eosinophils, and neutrophils has been established in incidence and onset of asthma symptoms. These factors cause direct stimulation of the smooth muscles of alveolar wall and secretion of histamine from mast cells, mucus production, and reaction with alpha 1-protease inhibitor. According to studies by Hatch, vitamin C is the most important antioxidant that is present in surfactant fluid, and plays a protective role against both internal and external oxidants including cigarette and air pollution. Accordingly, the theory of asthma linked to oxidant-antioxidant unbalance is propounded. Indeed, according to our study, asthma patients had lowered serum vitamin C levels and thus greater oxidative stress (35, 36). In another study, an inverse relationship was found between biological markers of infection (CRP, Alpha 1 antichymotrypsin), and vitamin C level, which can suggest that in asthma patients, vitamin C causes incidence of a proper biological response to viral infections (36).

In the study by Cook et al., a significant relationship was found between wheezing and reduced consumption of fruits containing vitamin C in 2,650 children in England. Note that this study had been performed as questionnaire and by the mothers of children, and may have had confounding factors. On the other hand, in our study, the serum level of this vitamin was examined, and no question was asked about diet from the family (which can be a confounding factor in its own right) (37). In the present study, there was a significant difference between the intervention and control groups regarding the mean serum level of vitamin C. However, in the study by Picado et al., this relationship did not exist (38). Also, in the study by the American National Health and Nutrition Institute, a significant relationship was found between low serum levels of vitamin C and incidence of asthma (28). Nevertheless, in this study, other variables including race, weight, and exposure to cigarette smoke had also been considered, which were not captured in our study. On the other hand, in our study, there was a significant relationship between vitamin C

consumption and tachypnea as well as wheezing in both intervention and control groups. It also caused diminished duration of hospitalization in the case group, while this had not been tested in the study by the American National Health Institute (28). In the present study, the severity of respiratory distress (including wheezing and tachypnea) improved noticeably in 2-12-year-old children who had consumed vitamin C as compared to the control. This means that vitamin C during 2-12 years of age can have considerable effects on improving respiratory distress (tachypnea and wheezing). The low serum levels of vitamin C at the beginning of hospitalization in the intervention group and its elevation following administration of oral vitamin C and improvement in symptoms and wheezing as well as reduced duration of hospitalization in the intervention group compared to the control, can suggest the effect of vitamin C prescription on these patients. Further, the serum level of vitamin C at the beginning of hospitalization did not differ significantly between the two groups, but following oral vitamin C administration, a significant difference was found. In addition, it can be concluded that vitamin C deficiency leads to aggravation of asthma attack symptoms and increased duration of hospitalization among 2-12-year-old children. Since the present study was pilot, subsequent research with a larger sample size is recommended so that more valid information can be found in this regard. In future studies, in addition to the serum level of vitamin C, questionnaire can be used about the diet, while also investigating other risk factors intensifying asthma through the parents of children.

5- CONCLUSION

Oral vitamin C prescription in children referring with acute asthma symptoms led to improved respiratory status (tachypnea and wheezing) among 2-12-year-old children. It was also effective in reducing the duration of hospitalization for the children, where this duration was shorter in the group receiving the vitamin. According to the present study, it is suggested that prescription of oral vitamin C supplement be considered for children who have been hospitalized because of asthma attacks, in addition to the asthma pharmacotherapy.

6- CONFLICT OF INTEREST: None.

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