Journal of Clinical and Nursing Research, 2023, Volume 7, Issue 1
http://ojs.bbwpublisher.com/index.php/JCNR
ISSN Online: 2208-3693
ISSN Print: 2208-3685

A Meta-Analysis of the Effectiveness of Vitamin C in the Prevention and Treatment of Childhood Upper Respiratory Tract Infections

Haitham Saeed, Mohamed EA Abdelrahim*

Clinical Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef 62514, Egypt

***Corresponding author:** Mohamed EA Abdelrahim, mohamedemam9@yahoo.com

Abstract: *Background:* The effectiveness of vitamin C in the prevention and treatment of pediatric upper respiratory tract infections was evaluated in a meta-analysis. *Methods:* A total 2,573 children with upper respiratory tract infections were included in the meta-analysis, 1,280 of whom received vitamin C and 1,293 who received control medication. The analysis of findings related to the studies included was done through random or fixed effects model to determine whether vitamin C supplementation could stop and control upper respiratory tract infections in children using mean difference (MD) with 95% confidence intervals (CIs). *Results:* On average, vitamin C-treated children had fewer upper respiratory tract infection bouts, their illness lasted shorter (MD -0.84; 95% CI -1.47 to -0.20, P = 0.009), and they were less contagious than the control. *Conclusions:* The number of episodes and illness duration of upper respiratory tract-infected pediatric subjects were considerably reduced in the intervention group (vitamin C) compared to the control. Due to the small sample size in four of 11 studies and the limited number of studies included for comparison, the outcomes should be carefully examined.

Keywords: Vitamin C; Upper respiratory tract infection; Number of episodes; Duration of illness

Online publication: January 5, 2023

1. Introduction

Recommendations will be made based on the prognostic values that reflect the efficacy and safety of vitamin C for the prevention and treatment of upper respiratory tract infections in children. We will also recommend potential areas for further research to aid our investigation.

The most prevalent reason for pediatric doctor visits is upper respiratory tract infections. Viruses that cause upper respiratory tract infections are often self-limiting and would clear within seven to ten days without any treatment [1]. However, in bacterial infections, such as acute bacterial otitis media, acute bacterial sinusitis, or lower respiratory tract infection, antibiotics are required [2]. When it comes to preventing upper respiratory tract infections, the use of vitamin C has been recommended since 1940. Antioxidant L-ascorbic acid protects host cells from oxidative stress caused by infection.

Given that phagocytes and lymphocytes have higher levels of L-ascorbic acid than plasma does, it stands to reason that vitamin C has a vital role in the function of immune system cellular components. Vitamin C has been widely used ever since Pauling's clinical experiments proved that vitamin C suppresses upper respiratory tract infection and improves its symptoms in the 1970s [3]. However, this protective effect of vitamin C supplementation has not been confirmed in subsequent trials [4]. Since they spend so much time in public and have such undeveloped sinus and immune responses, children up to 18 years make up a

unique subpopulation that is at risk for upper respiratory tract infection. The protective and therapeutic properties of vitamin C in this age range have been the subject of far too few investigations. There was a meta-analysis in 2013 that investigated vitamin C's effectiveness in the prevention and management of common cold [5]. However, the evaluation did not specifically assess the effect of vitamin C on the occurrence of upper respiratory tract infection in children and adolescents. The fact that vitamin C supplementation is still recommended or used as a self-medication in case of upper respiratory tract infection in children necessitates a re-evaluation of its use. Therefore, this study aimed to determine the effectiveness of vitamin C in the treatment and prevention of pediatric upper respiratory tract infections.

2. Methods

2.1. Study design

The epidemiological statement was subjected to a meta-analysis with a pre-established study process, which now also incorporates research investigations [6]. Numerous search engines, including OVID, Embassy, PubMed, and Google Scholar, were utilized to gather and evaluate data.

2.2. Data pooling

Through randomized controlled trials, observational studies, and retrospective investigations, the effectiveness of vitamin C in the prevention and treatment of pediatric upper respiratory tract infections was investigated. No factors other than human research in any language or dialect were taken into account. The total number of individuals that may be included was unaffected by the study's size. The meta-analysis excluded review papers, letters, comments, and studies that did not offer a way to quantify an association. The entire process of the investigation is shown in **Figure 1**.

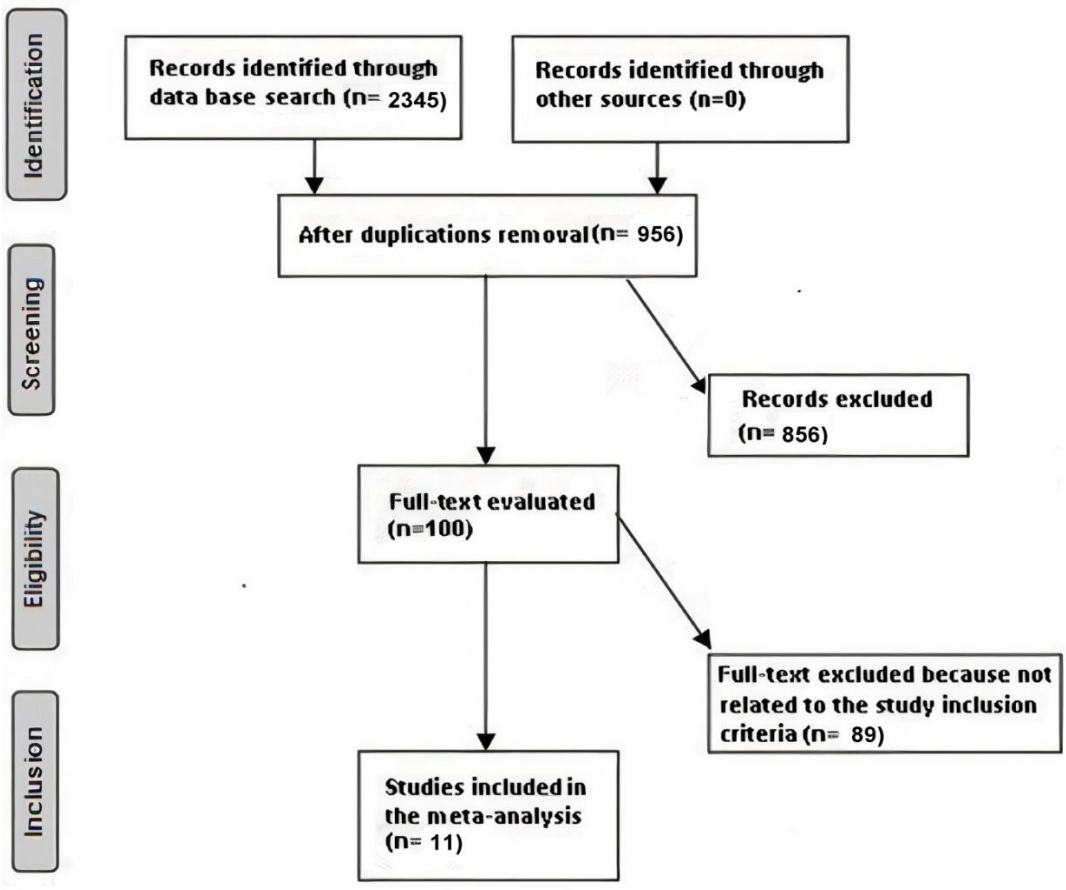

Figure 1. A flowchart of the study process

The publications were included in the meta-analysis if the following criteria were satisfied: (1) an observational study, a randomized controlled trial, or a retrospective or prospective study; (2) the primary emphasis of the study was on children with upper respiratory infection; (3) vitamin C was included as a significant part of the therapeutic regimen; (4) as a control, vitamin C was used in the study.

The exclusion criteria were as follows: (1) a dearth of methods for analyzing how vitamin C affects childhood upper respiratory tract infections; (2) research involving a control group of children and children who received an alternative supplement to vitamin C; (3) studies without comparative outcomes.

2.3. Identification

According to the PICO model, we created a protocol of search techniques. P (population) was made up of pediatric subjects who had upper respiratory tract infection. There was no constraint on the study design or the number of episodes or durations that may be studied. I (intervention) was represented by vitamin C; C was the comparison between the administration of vitamin C and placebo; and O was the outcome [8].

We scoured several databases, including Embase, Cochrane Library, OVID, PubMed, and Google Scholar, for references concerning upper respiratory tract infections, vitamin C, number of episodes, and duration until March 2022, using a combination of keywords and comparable phrases, as shown in **Table 1**. We excluded duplicate studies and examined the titles and abstracts to include studies that have found a link between vitamin C and upper respiratory tract infection prevention.

Table 1. Characteristics of the selected studies for meta-analysis

Study	Country	Total	Vitamin C	Control
Ritzel, 1961 [9]	German	48	17	31
Coulehan, 1974 [10]	USA	382	190	192
Coulehan, 1976 [11]	USA	259	131	128
Miller, 1977 [12]	USA	88	44	44
Ludvigsson, 1977 [13]	Sweden	615	304	311
Miller, 1978 [14]	USA	431	220	211
Bancalari, 1984 [15]	Switzerland	62	32	30
Cohen, 2004 [16]	Israel	328	160	168
Constantini, 2011 [17]	Finland	39	21	18
Kumari, 2020 [18]	Pakistan	150	75	75
Garaiova, 2021 [19]	UK	171	86	85
Total		2,573	1,280	1,293

2.4. Screening

The study period, year of publication, first author's last name, place of study, and study design were all used to condense relevant data: both study-related and subject-related characteristics in consistent form; qualitative and quantitative evaluation methods; information source; number of children; population type; demographics; categories; characteristics of the clinical and treatment services provided; and evaluation of outcomes [20]. Whenever data were available from a single trial assessing the effectiveness of vitamin C in the prevention and treatment of pediatric upper respiratory tract infections, these items were extracted separately. Methodological quality assessment was performed by assessing the risk of bias for each individual study through the "risk of bias tool" from Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0) [21].

The following criteria were used to grade and categorize the studies included: if all quality criteria were met, the study was considered to have a low bias risk; if some (one or more) of the quality criteria were only partially met or unclear, the study was associated with significant bias risk; if one or more of the criteria were not met or included, the study was associated with substantial bias risk. Any discrepancies were resolved after the original content was re-evaluated.

2.5. Eligibility and inclusion

Vitamin C was compared to a control to see how well it stopped and managed pediatric upper respiratory tract infections. The summary of the findings focused on comparing vitamin C to the control. Only studies comparing the effectiveness of vitamin C to the control group were included in the sensitivity analyses. Subcategory and sensitivity analyses compared vitamin C to a control.

2.6. Statistical analysis

In this meta-analysis, a fixed or random effects model was used to calculate the mean difference (MD) and 95% confidence interval (CI). A scale of 0% to 100% was used to calculate the I^2 index. No, low, moderate, and high heterogeneity were represented by 0%, 25%, 50%, and 75%, respectively [22]. In order to generate a forest plot, we employed the random effects model when I^2 was greater than 50% and the fixed effects model when I^2 was less than 50%. A subclass analysis was accomplished by stratifying the initial examination for result categories. Differences between subcategories were deemed statistically significant with a *P* value of 0.05 [7]. *P* values were obtained using a two-tailed test. Statistical evaluations and graphs were created using Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

3. Results

A total of 2,573 children with upper respiratory tract infections were included in the research, among which 1,280 received vitamin C and 1,293 received a placebo.

At the commencement of the study, the sample size ranged from 39 to 615 youngsters. In six studies, data were provided according to the number of episodes, while in 10 studies, data were reported according to duration.

A total of 11 articles out 2,345 relevant studies between 1961 and 2021 met the inclusion criteria and were included in the meta-analysis [9-19].

As shown in **Figures 2** and **3**, compared to the control group, vitamin C-treated children had significantly fewer episodes of upper respiratory tract infections (MD -0.84; 95% CI -1.47 to -0.20, *P* = 0.009) and shorter duration of illness (MD -1.57; 95% CI -2.32 to -0.82, *P* = 0.001), with high heterogeneity (I^2 = 97%, 85%).

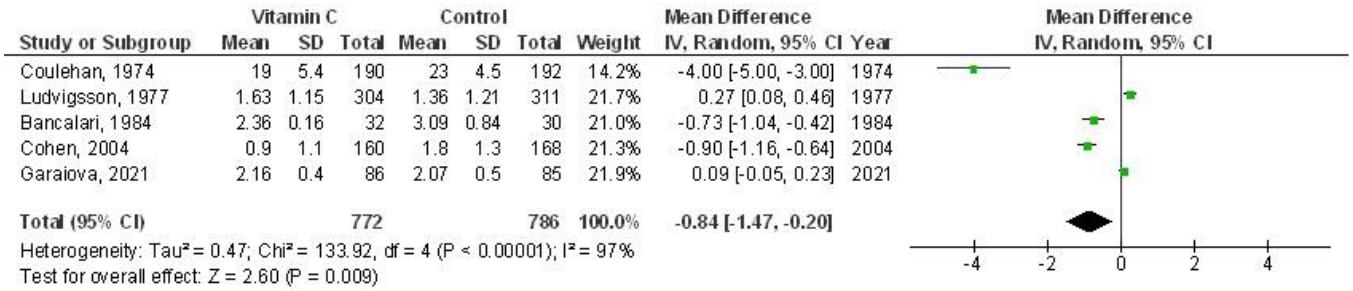

Figure 2. A forest plot showing how vitamin C affects the number of episodes and outcomes in children with upper respiratory infections when compared to the control group

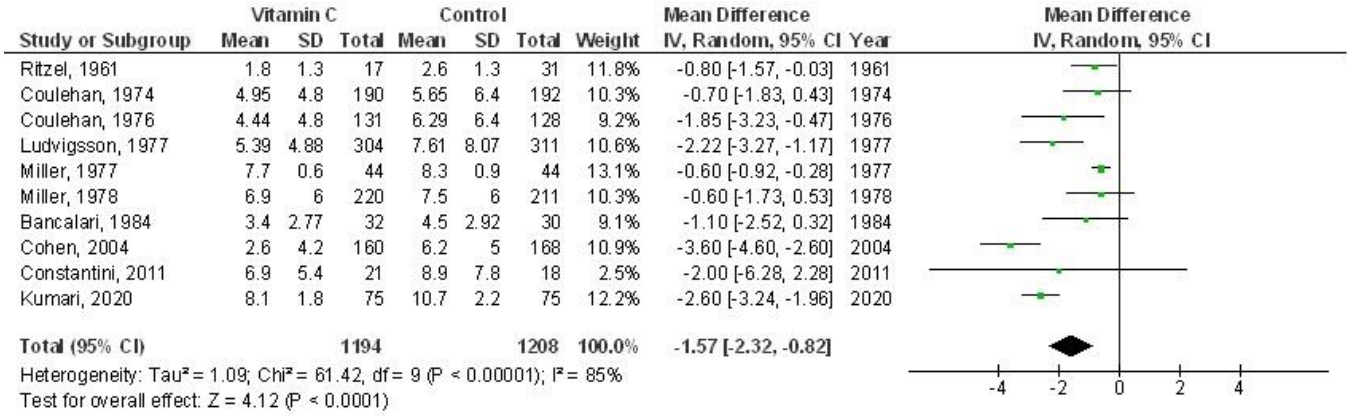

Figure 3. A forest plot of the relationship between vitamin C and the incidence of outcomes for duration in children with upper respiratory tract infections

Stratified models could not be used to examine the influence of individual considerations, such as gender, age, and ethnicity, on the comparison of findings because no data exist for these variables. Most of the randomized controlled trials included in this meta-analysis had low methodological quality, no selective reporting bias, and insufficient outcome data.

4. Discussion

Pediatric subjects with upper respiratory tract infections were included in this meta-analysis, with 1,280 receiving vitamin C and 1,293 receiving a placebo [9-19]. The number of episodes and duration of illness of pediatric upper respiratory tract infection were considerably reduced in the intervention group (vitamin C) compared to the control. More future trials are needed to confirm these findings. Since four of the 11 studies had a sample size of fewer than 100 participants, the results should be interpreted with caution.

Vitamin C has been widely used for COVID-19 infection, as have other treatments for upper respiratory tract infections of a similar nature [23]. Vitamin C supplementation in children under six has not been extensively researched. However, as revealed in a randomized controlled study by Cohen [14], a small dose of vitamin C is effective in this age group. This finding is also supported by a pilot study by Garaiova [10]. In the first trial, vitamin C was associated with echinacea and propolis, but in the second trial, it was associated with probiotics. Echinacea was found to be ineffective in decreasing the incidence and duration of upper respiratory tract infections; probiotics, on the other hand, showed better effects than placebo at stopping these illnesses with a low indication level [24-26]. These results are difficult to comprehend. When it comes to upper respiratory tract infections, the approach of one-size-fits-all is irrelevant. If a child's rhinitis is accompanied by mucopurulent discharge, which could be mistaken for bacterial etiology, parents may request for medications. The six-day decrease in upper respiratory tract infections by 1.6 days is likely due to less unnecessary prescriptions of antibiotics and other medications, including antihistamines and decongestants. This is particularly true for young children, who on average suffer 6–8 episodes of upper respiratory tract infection each year [27]. Vitamin C supplementation may act as an adjuvant to lessen the frequency and duration of infection for parents who find it difficult to accept the high prevalence of infections. Children as young as three years old may offer a valuable insight on the immune system's development.

According to this meta-analysis, vitamin C has a beneficial effect on the treatment and prevention of upper respiratory tract infections in children [28-38]. It will take more investigations to prove these potential connections and determine how vitamin C affects the outcomes compared to the control. These studies call for larger, more consistent samples. Previous research has suggested that increasing vitamin C intake can

help reduce both the frequency and duration of episodes [9, 39-41]. Further randomized controlled trials are needed to evaluate these associations and other factors, including gender, age, ethnicity, *etc*., as our meta-analysis was unable to determine whether age and ethnicity have any impact on the outcomes.

Compared to the control group, vitamin C-treated children had considerably fewer episodes and a shorter duration of illness.

5. Limitations

Considering that many papers were not included in this meta-analysis, there is a possibility of selection bias in this study. However, the studies that were excluded from our meta-analysis did not meet our inclusion criteria. Furthermore, the sample sizes of four of the 11 studies were below 100. The findings were also unrelated to race, age, or gender, thus leaving another unresolved question. Although vitamin C supplementation can help prevent and treat upper respiratory tract infections in children, this study relied on data from previous research, which could have been skewed due to insufficient information. Characteristics such as gender and age could be bias-inducing factors, and previous unpublished studies and data shortages may have skewed the findings of this study.

6. Conclusions

Compared to the control, vitamin C significantly decreased the frequency of upper respiratory tract infection episodes and the duration of illness in children. More studies are needed to confirm the two conclusions. The fact that only a few investigations were included in the meta-analysis and four of the 11 studies had small sample sizes necessitates a careful examination of the results.

Disclosure statement

The authors declare no conflict of interest.

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