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Efficacy and safety of vitamin C in the management of acute respiratory infection and disease: A rapid review

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ABSTRACT

Brief overview: Current evidence from published systematic reviews indicate that oral intake of vitamin C may assist with symptoms of acute viral respiratory infections (ARI) by reducing fever and chills, relieving chest pain and assist in reducing symptoms of common cold-induced asthma. Intravenous (IV) vitamin C administration may reduce the need for vasopressor support and the duration of mechanical ventilations in critically ill patients in hospital. COVID-19 has similar signs and symptoms of ARI. Further studies involving patients with COVID-19, either through administration of oral vitamin C in mild cases or IV vitamin C in critical cases, would be advantageous to examine if it is safe and efficacious.
Verdict: Oral vitamin C may assist with the symptoms of acute respiratory viral infections (ARI) and common cold-induced asthma but no studies have been identified justifying oral vitamin C for the prevention or treatment of coronavirus infections including COVID-19. When taken at onset of ARI, oral vitamin C may reduce the duration of symptoms including fever, chest pain, chills and bodily aches and pains. It may also reduce the incidence of hospital admission and duration of hospital stays. For individuals admitted to hospital with community-acquired pneumonia, vitamin C may improve respiratory function in more severe cases. No major adverse events nor interactions were reported by either method of administration. However, there is an absence of high quality, contemporary clinical research examining this topic. Current evidence suggests further studies are needed to better understand the value of both oral and IV vitamin C for ARI, including COVID-19.

1. Background

Vitamin C is an essential micronutrient involved in various cellular functions of both the innate and adaptive immune systems. Vitamin C accumulates in phagocytic cells, such as neutrophils, through which it can enhance chemotaxis, phagocytosis, and generation of reactive oxygen species. Vitamin C is also involved with apoptosis and clearance of used neutrophils from sites of infection by macrophages thereby reducing potential tissue damage. Vitamin C also supports differentiation and proliferation of B- and T- cells [1].

Vitamin C was proposed as a potential useful agent for coronaviruses in 2003 when the SARS coronavirus was active [2] based on available evidence that vitamin C affects severe viral respiratory tract infections. Hemila [2], who has continued researching vitamin C for ARI, presented this hypothesis based on the evidence of vitamin C's non-specific effects on severe viral respiratory tract infections. This raises queries regarding vitamin C's potential application in the management of COVID-19.

2. Search strategy

2.1. Research question

What is the effect of Vitamin C on acute respiratory tract infections in adults when administered at the onset of symptoms?

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2.2. Inclusion/exclusion criteria

2.2.1. Inclusion criteria

- Systematic review of clinical trials
- No age restrictions
- Administration at onset of symptoms of acute respiratory tract infection
- Oral or intravenous administration of Vitamin C

2.2.2. Exclusion criteria

- Prophylactic administration

2.3. Databases

Medline (Ovid), Embase (Ovid), AMED (Ovid), CINAHL (EBSCO)
Search terms (examples)

2.3.1. Ovid medline

(Systematic Review/ or Meta-analysis/ or Systematic Review as Topic/ or Meta-Analysis as Topic/ or Review Literature as Topic/ or (Systematic review or meta analy$ or metaanaly$).ti,ab,kw.) not (comment/ or letter/ or editorial/) AND Influenza, Human/ or Influenza A Virus, H1N1 Subtype/ or Influenza A virus/ or Influenza A Virus, H3N2 Subtype/ or Middle East Respiratory Syndrome Coronavirus/ or respiratory tract infections/ or bronchitis/ or common cold/ or exp sinusitis/ or (Influenza or H1N1 or MERS−COV or flu or Bronchit* or sinusit* or rhinosinusit* or rhinit* or common cold or (respiratory adj2 (infect* or illness or symptom* or acute or virus* or disease))).ti,ab,kw. AND exp Ascorbic Acid/ or (ascorbic acid or Vitamin c).ti,ab,kw (Table 1).

2.3.2. CINAHL EBSCO

PT systematic review OR PT meta-analysis or (MH "Systematic Review") OR "systematic review" OR (MH "Cochrane Library") OR (MH "Meta Analysis") OR TX meta analy* OR TX metaanaly* OR TX systematic* review AND (MH "Influenza+") OR "Influenza" OR (MH "Influenza A Virus+") OR (MH "Influenza, Pandemic (H1N1) 2009") OR (MH "Influenza A H5N1") OR (MH "Influenzavirus C") OR (MH "Influenza B Virus") OR (MH "Influenza A Virus, H1N1 Subtype") OR (MH "Influenza, Swine") OR (MH "Influenza, Human+") OR (MH "Influenza, Seasonal") OR (MH "Influenza A Virus, H5N1 Subtype") OR (MH "Influenza A Virus, H3N2 Subtype") OR (MH "Cold+") OR (MH "Rhinitis") OR (MH "Rhinosinusitis") OR (MH "Severe Acute Respiratory Syndrome") OR (MH "Sinusitis") OR (MH "Bronchitis") OR (MH "Bronchitis, Acute") OR (MH "Common Cold") OR (MH "Respiratory Tract Infections") OR TX influenza OR TX H5N1 OR TX Common Cold OR TX Rhinitis OR TX Rhinosinusitis OR TX Bronchitis OR TX H3N2 OR (TX Respiratory N2 (infect* OR illness* OR symptom OR acute OR virus* OR disease*)) AND (MH "Ascorbic Acid") OR TX “vitamin c” OR TX “Ascorbid adic”

2.4. Critical appraisal

The critical appraisal tool used to assess the studies in this rapid review was the BMJ Best practice, appraising systematic reviews (https://bestpractice.bmj.com/info/toolkit/learn-ebm/appraising-systematic-reviews/).

3. Rapid review results

A search conducted across 4 databases identified 141 review articles. Following the removal of 34 duplicates, 107 review articles were screened by title and abstract for relevance to the study question. Of these, 36 full-text literature reviews were assessed for eligibility against the pre-defined inclusion criteria. A total of 31 articles were removed due to not meeting one or more of the criteria as follows: different patient population (4), study design (14), intervention type (3), not an adult population (3), study setting (1), not written in English (1), indication (2), reviews of reviews (3), the remaining 6 articles were included in this rapid review.

3.1. Critical appraisal

From the appraisal, three of the five systematic reviews met all the requirements [4,5,7]. One systematic review met the majority of the requirements with the reviewers unable to verify if combined primary studies and combined statistical results were correct [6]. The last review was considered to have a lower level of evidence for a systematic review but was still adequate [3]. Overall, the level of evidence for the reviews chosen were adequate.

3.2. Summary of findings

All five studies were systematic reviews of randomised controlled trials (RCTs) [1–4]. Two of the studies included a meta-analysis of the included study data [2,4]. The study population and size, type of respiratory condition, form and dose, and administration route of vitamin C varied across the studies reviewed. The measurement outcomes reviewed by each study varied and were specific to the study focus.

Hemila’s 2004 systematic review included eight double-blind randomised-controlled trials, two controlled trials and two studies with poorly defined designs conducted between 1999 and 2002. A total of 1997 participants who were military personal and 587 athletics students in crowded lodgings and marathon runners were allocated to receive vitamin C with doses ranging from 0.05 to 2 g/d for 7 days to 6 months. The severity and duration of respiratory infections were measured in addition to the number of hospital admissions. Overall, positive findings were reported for the severity of respiratory tract infections. The authors suggested the results should be interpreted with caution due to the heterogeneity in study designs including formulation, dose, dietary intake of vitamin C, and the degree of participant’s physical exertion [1].

Hemilia’s 2013 meta-analysis included 3 controlled clinical trials involving 79 (children and adults) evaluating the efficacy of ascorbic acid as single or multiple oral doses for different lengths of time (1 g/d for 14 weeks, 2 g/d one dose at two time points, 5 g/d for 2 weeks) in reducing the incidence and severity of commoncold induced asthma. The primary endpoints across the studies were frequency of asthma attacks, sensitivity to asthma symptoms scores, peak expiratory flow, histamine sensitivity and severity of colds. Significant reductions in the incidence RR = 0.22 (0.06 to 0.81) and severity of asthma attacks RR = 0.22 (0.06 to 0.81) and a 52 % reduction in participants sensitive to histamine sensitivity as measured by PC20 levels [2].

Hemila and Chalkers 2013 systematic review included 29 trial comparisons involving a total of 11,306 participants to identify whether vitamin C reduces the incidence, the duration or severity of the common cold. The studies included were from inception to 2013. Collectively the studies involved 10,708 participants from the general community and 598 participants which exercised in extreme conditions. Of the 31 comparisons analysed on people taking vitamin C it was found to reduce the duration of the common cold and the severity of symptoms. No consistent effects were seen on studies evaluating the use of vitamin C during the common cold on duration or severity [3].

Hemila and Louhiala [5] systematic review included six controlled trials comprising a range of populations (elderly,

Table 1
Summary of systematic reviews of vitamin C in the management of acute respiratory infection and disease.

Author	Year	Type of Review	Review duration	Types of Studies included	Databases Used	Intervention Searched	Participants included (*condition of interest*)	Publication years of including studies	Number of Studies included	The number of Types of Studies included	Administration of Vitamin C	Total number of participants in the Review	*Dose*	Control or Placebo	N in intervetion and placebo	Measure of Outcome	Outcome
Identification		Methods							Methods and Dose							Outcomes	
Hemila	2013	Meta-analysis	Inception to September 2013	Intervention studies (randomised/ non-randomised; placebo-controlled/ non-placebo-controlled)	Medline (OVID), Scopus, Cochrane Central Register of Controlled Trials	oral or intravenous vitamin C (ascorbic acid or its salts) as a single or multiple doses	children and adults of either sex at any age (*common cold-induced asthma*)	1980–1990	3	2 x randomised-double blind placebo-controlled trial (1 x cross-over) and 1 x self-controlled study	Not specified	N=79	1 g/day; 5 g/day; 2 g/single dose	Placebo x 2; no control x 1	Vit C (22 + 23 + 9 = 54); placebo (19 + 23 = 42)	Frequency of asthma attacks; sensitivity to histamine; asthma symptom score; PEF; PC20	Incidence of all asthma attacks RR = 0.22; Incidence of severe and moderate asthma attacks RR = 0.11 52 % decrease in proportion of participants sensitive to histamine No significant difference No significant difference 3.2 fold increase
Hemila	2004	Systematic review	1999–2002	Intervention studies (placebo-controlled/ non-placebo-controlled)	Medline, SCISEARCH, EMBASE	unrestricted	military personnel; students in crowded lodgings; marathon runners (*respiratory infections)*	1942–1996	12	8 x randomised, double-blind, placebo controlled trial; 2x non-placebo-controlled trial; 2 x poorly described methodology	Oral; dietary fortication	N=1394	0.05–2 g/day for 7days - 6 months	Placebo x 8; Non-placebo x 2; Unclear x 2	(vit c = 561; control = 833)	Severity of colds duration of colds (days); Incidence and duration of specific symptoms; hospital stays (days) hospital admissions	1.87 vs 1.97 [p = .012] No significant difference Constitutional symptoms: 0.8 v 2.4 days [p = .045], 8v21 case [p = .006]. Other symptom categories not significant 10.1 v 16.7 [p = .012] 18v83 [p = .09]
Hemila and Chalker	2013	Systematic review	2010–2012	Intervention studies (placebo-controlled only)	CENTRAL, MEDLINE, Embase, CINAHL, LILACS, Web of Science	Minimum of 0.2 g/day vitamin C	Children and adults of either gender and any age (*common cold*)	1950–2001	20 (43 additional studies reported prevention rather than treatment outcomes)	17 x placebo-controlled trials in community; 3 placebo-controlled laboratory trials	Oral	N = 3249	1–8 g/day for 1–4 days	Placebo	Vit C = 1968; Control = 1281	Duration of colds Mean days off work/ school (severity)	No statistical significance Diff: -0.08 [p = .048]
Hemila and Louhiala	2017	Systematic review	1950–2011	Intervention studies (placebo-controlled/ non-placebo-controlled)	Cochrane Central Register of Controlled Trials 2011, Medline, EMBASE, Web of Science	Vitamin C only (ascorbic acid or its salts) to one trial group, orally or IV as a single dose (allowed in treatment studies) or multiple doses, with no other nutrient substances	No age restriction	1970–1994	5 (3 x prophylactic and 2 x treatment trials)	2 x 'quasi-placebo control'; 2 x randomised double-blind placebo-controlled; 1 x no placebo, blinding not described	1 x oral dietary fortification; 4 x not specified	N = 2532	0.05 to 0.3 g/day for 6 months; 0.2 g/day for up to 4 weeks; 0.3 g/day for unspecified duration; 2 mg per 2000 antibiotic units (0.5–1.6 g/day) or 1 mg per 2000 antibiotic units (0.25 to 0.8 g/ day) for unspecified duration	2 x no placebo; 1 x low-dose vit. C used as placebo in primary comparison; 2 x placebo	Vit C = 878; control 1282; placebo 372	Community-acquired: Severity of pneumonic episodes Community-acquired: Duration of pneumonic episodes Community-acquired:	Reduced severity score (-2.31) at four weeks (p = .053) for patients with higher respiratory scores on admission −4.0 days in high vitamin C compared with low vitamin C arm (p < .0001) No evidence available

Table 1 (*Continued*)

Author	Year	Type of Review	Review duration	Types of Studies included	Databases Used	Intervention Searched	Participants included (*condition of interest*)	Publication years of including studies	Number of Studies included	The number of Types of Studies included	Administration of Vitamin C	Total number of participants in the Review	*Dose*	Control or Placebo	N in intervetion and placebo	Measure of Outcome	Outcome
																Death caused by pneumonia Hospital-acquired pneumonia	No evidence availabile
Ran et al	2018	Systematic review and meta-analysis	Inception to March 2018	randomised controlled trials	PubMed, Cochrane Library, Elsevier, CNKI, VIP databases, WANFANG	vitamin C, added as a regular supplement or administered as needed when cold symptoms developed	definitive diagnosis of common cold based on laboratory examination, clinical signs, or reported symptoms; no limitation in age, sex, occupation		9	9 x randomised placebo-controlled trials	Oral	n = 5722 + 1 study n = not reported	from 0.67 g per 4 h (4 g over 24 h) to max 10 doses; 1500 mg on day 1 after 500 mg/day; max8 g on day 1	all studies used unspecified placebo	Vit C 2564; control 2076; 1082 unspecified; 1 study not reported	Mean duration; nasal congestion or runny nose; sore throat; aching limbs and muscles; mental depression;	no statistical significance
																Fever	significantly better at reducing fever by about 0.5 days (MD = -0.45, 95 % CI [-0.78, -0.11], and P = 0.009)
																Chest pain	higher efficacy in relieving chest pain (MD = -0.40, 95 % CI [-0.77, -0.03], and P = 0.03)
																Chills	better at relieving chills by about 8.5 h (MD = -0.36, 95% CI [-0.65, -0.07], and P = 0.01)
																Being confined Indoors	reduced confinement indoors by about 6.5 h (MD = -0.27, 95% CI [-0.46, -0.08], and P = 0.004)
Zhang and Jativa	2018	Excluded as participant did not have ARI															
Heimer	2009	Excluded as it is a review of reviews															
Hemila	1994	Excluded as superceded by Hemila 2013															
Hemila	1999	Excluded as supplementation was initiated with healthy subjects															
Nahas and Balla	2011	Excluded as the vitamin C part was a review of reviews															
Rondanelli et al	2018	Excluded as it is a narrative review															

boarding school male students, burns patients, and military personnel) and varied study designs (non-placebo and placebo-controlled studies). Five studies involved the oral administration or vitamin C (200 mg–3000 mg) in either the prevention (n = 3) or treatment (n = 2) of community -acquired pneumonia and 1 study administered intravenous vitamin C (66 mg/kg/h) during the 24 h after admission to a burns unit to prevent hospital-acquired pneumonia.

The three trials examining continuous oral vitamin intake reported 37 cases of community-acquired pneumonia amongst 2335 people and found that vitamin C reduced the incidence of pneumonia by 80 %. The two treatment trials involving 197 community-acquired pneumonia patients and one prophylactic trial recorded 13 cases of hospital-acquired pneumonia across 37 patients. Rans 2018 meta-analysis including nine RCTs and 3796 participants with a definitive diagnosis of the common cold based on laboratory examination, clinical signs, or reported symptoms from a broad demographic and conducted between 1950 and 2001, evaluating the effectiveness of vitamin C doses ranging from 500 mg to 8 g per day in the treatment of the common cold symptoms. No statistically significant effects were observed for nasal congestion or runny nose, sore throat, aching limbs and muscles or mental depression. Statistically significant improvements were identified for the symptoms of fever (p = 0.009), chest pain (p = 0.03) and chills (0.01) and being confined in doors was reduced by half a day (p = 0.004) [4].

4. Clinical significance

The evidence from this rapid review has identified that oral vitamin C may assist with the symptoms of acute respiratory viral infections (ARI) and common cold-induced asthma but no studies have been identified justifying oral vitamin C for the prevention or treatment of conditions similar to COVID-19. When taken at onset of ARI, oral vitamin C may reduce the duration of AR symptoms including fever, chest pain, chills and bodily aches and pains. It may also reduce the incidence of hospital admission and duration of hospital stays. Evidence related to IV vitamin C from this literature review for COVID-19 or similar conditions is very limited due to the reviews not specifying IV versus oral administration. However, from the studies included in these reviews, further investigation is warranted to examine the effect of IV vitamin C as an adjunct to current medical treatment in acute COVID-19 patients. In addition, oral administration at onset of symptoms to reduce duration and severity of COVID-19 infection also warrants further investigation. Current evidence suggests further studies are needed to better understand the value of both oral and IV vitamin C for ARI, including COVID-19.

Disclaimer

This article should not replace individual clinical judgement. The views expressed in this rapid review are the views of the authors and not necessarily from the host institutions. The views are not a substitute for professional medical advice. This is a rapid review of systematic reviews, and it should be noted that the original research papers included in each of the reviews included here, were not individually examined by the authors of this rapid review.

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