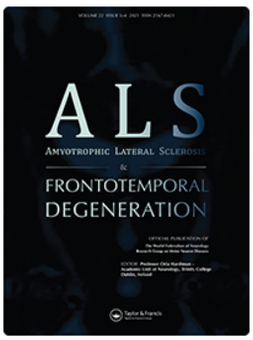

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iafd20

ALSUntangled #62: vitamin C

Richard Bedlack, Paul Barkhaus, Greg Carter, Jesse Crayle, Christopher Mcdermott, Gary Pattee, Meraida Polak, Kristiana Salmon & Paul Wicks

To cite this article: Richard Bedlack, Paul Barkhaus, Greg Carter, Jesse Crayle, Christopher Mcdermott, Gary Pattee, Meraida Polak, Kristiana Salmon & Paul Wicks (2021): ALSUntangled #62: vitamin C, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, DOI: 10.1080/21678421.2021.1946088

To link to this article: https://doi.org/10.1080/21678421.2021.1946088

Published online: 30 Jun 2021.

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2021; 0: 1–4

RESEARCH ARTICLE

ALSUntangled #62: vitamin C

RICHARD BEDLACK[1], PAUL BARKHAUS[2], GREG CARTER[3], JESSE CRAYLE[4], CHRISTOPHER MCDERMOTT[5], GARY PATTEE[6], MERAIDA POLAK[7], KRISTIANA SALMON[8] & PAUL WICKS[9]

[1]Department of Neurology, Duke University, Durham, NC, USA, [2]Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA, [3]Department of Rehabilitation Medicine, University of Washington, Seattle, WA, USA, [4]Department of Neurology, Washington University in St Louis School of Medicine, St Louis, MO, USA, [5]Department of Neuroscience, The University of Sheffield Institute for Translational Neuroscience, Sheffield, United Kingdom of Great Britain and Northern Ireland, [6]Department of Neurology, Neurology Associates, Lincoln, NE, USA, [7]Department of Neurology, Emory Healthcare, Atlanta, GA, USA, [8]Department of Neurology, McGill Centre for Research in Neuroscience, Montreal, Canada, [9]UIndependent Consultant, United Kingdom of Great Britain and Northern Ireland

ABSTRACT

Vitamin C is one of the most common supplements taken by people with ALS. As an antioxidant, it has a plausible mechanism for slowing disease progression and there are some flawed pre-clinical studies and case reports suggesting benefit. However, a small human trial showed no benefit. Given this negative trial, we do not currently advise vitamin C as an ALS treatment.

Keywords: *Vitamin C, acorbic acid, ascorbate, clinical trials, therapy, models*

ALSUntangled reviews alternative and off-label treatments on behalf of people with ALS (PALS). Here we review the use of vitamin C (also called ascorbic acid or ascorbate) for which we have had 396 requests (1).

Overview

Vitamin C is a nutrient that plays essential roles in our response to infections and oxidative stress, and in the production of collagen, myelin, carnitines, neurotransmitters and peptide hormones (2,3). Humans cannot synthesize vitamin C and therefore must obtain it from their diets (2). Vitamin C deficiency (blood levels <11 umol/L) is surprisingly common (4,5). Severe deficiency of vitamin C results in scurvy, a rare condition characterized by collagen weakening, poor wound healing and susceptibility to infections (2). The consequences of milder deficiency may include increased susceptibility to infections (2,6), depression and cognitive impairment (3,7).

Whether vitamin C deficiency might contribute to the development of ALS remains speculative and controversial. One cross-sectional study from China found lower serum vitamin C levels in PALS compared to healthy controls (8). Another found higher CSF vitamin C levels compared to healthy controls (9). Pooled results from five large cohort studies demonstrated no relationship between vitamin C intake and the subsequent development of ALS (10). Nonetheless, perhaps due to its antioxidant effects and excellent safety profile, vitamin C is one of the most common supplements taken by people with ALS (11).

Mechanistic plausibility

Oxidative stress is believed to play an important role in ALS pathophysiology (12). In some (13,14) but not all (15) human studies, vitamin C treatment reduces serum biomarkers of oxidative stress including lipid hydroperoxides and isoprostanes (13,14). Vitamin C can cross the blood brain

Correspondence: Richard Bedlack, Department of Neurology, Duke University, Durham, NC, USA. E-mail: Bedla001@mc.duke.edu

(Received 18 May 2021; revised 14 June 2021; Accepted 16 June 2021)

ISSN print/ISSN online
DOI: 10.1080/21678421.2021.1946088

Table 1.. Table of evidence for vitamin C.

	Grade	Explanation
Mechanism	C	Vitamin C can reduce serum markers of oxidative stress but there is little evidence that it reduces these in brain or CSF
Pre-clinical	C	Two flawed studies in an ALS mouse model suggest benefits
Cases	B	2 patients with validated ALS diagnoses experienced validated improvements (ALS reversals) on cocktails of treatments including vitamin C
Trials	F	A small trial comparing vitamin C (along with 5 other antioxidants) to placebo showed no statistical benefit
Risks	B	Across many small human trials vitamin C appears safe. Patients with a history of renal insufficiency or kidney stones may be at an increased risk of new kidney stones.

barrier (16), but evidence of its antioxidant effect in brain or CSF biomarkers consists of a single study where it was used in combination with other antioxidants (17). Based on this limited and inconsistent human data, we assign a Table of Evidence (TOE) "Mechanisms" grade of C (Table 1). Full descriptions of our TOE and what the different grades mean can be found in reference 18.

Pre-clinical

We found two studies by the same group analyzing the effect of vitamin C in the G93A mSOD1 mouse model of ALS. In the first, treatment with a combination of oral vitamin C and trientine (a copper chelator) starting at day 45 resulted in a significantly delayed onset of neurological abnormalities and a prolonged time to total paralysis of hindlimbs (19). The second study examined the effects of these two agents individually, and also looked at treatment before versus after symptom onset (20). In this study, oral vitamin C treatment alone starting at day 50 (before symptoms started) did not affect the onset of neurological abnormalities or survival, but it did significantly delay time to total paralysis of hindlimbs (20). Vitamin C treatment started after symptom onset had no effect on any outcome measure (20). These studies are flawed by small sample sizes, lack of randomization or blinding, and use of treatments prior to the onset of symptoms. They have never been independently replicated. Based on these positive, flawed studies, we assign a TOE "Pre-Clinical" grade of C (Table 1).

Cases

In the PatientsLikeMe Community, 175 PALS reported taking vitamin C and 24 provided detailed treatment evaluations (21). Two reported "major" effectiveness, two "moderate", 1 "slight", 4 "none" and 15 "can't tell". Doses ranged between 400 mg and 100 g daily. No more details are available on these patients.

Within the cohort of "ALS Reversals" being studied at Duke University (22,23), two were taking vitamin C (along with many other treatments) during their recovery. Based upon these 2 cases with validated diagnoses and recovery associated with vitamin C treatment, we assign a TOE "Cases" grade of B (Table 1). As we have mentioned previously, an association between a treatment and an ALS Reversal does not mean one caused the other; there are many possible explanations for ALS Reversals (23).

Trials

We found only one prospective trial of vitamin C in ALS (24,25). Ten PALS were randomized to receive either vitamin C at 2,000 mg daily (along with five other antioxidants) or placebo for six months. A statistical analysis using analysis of variance (ANOVA) showed no effect of treatment on progression of a functional measure (the Appel Rating Scale, 24,25). Therefore we assign a TOE "Trials" grade of F (Table 1). This trial was underpowered to show a small treatment effect.

Dosing, risks and costs

Vitamin C is available in a wide range of doses and formulations, oral and intravenous. Optimal vitamin C dosing for PALS has not been established. For healthy adults, the National Institute of Health Office of Dietary Supplements recommends daily oral doses of 90–120 mg (26). One study showed that oral vitamin C at 1,000 mg daily was more effective than 500 mg daily in attenuating an exercise-induce marker of oxidative stress (protein carbonyls, 27). The sole vitamin C trial in PALS used an oral dose of 2,000 mg daily (24,25).

Reviews of oral (28) and intravenous (29) vitamin C studies suggest an excellent safety profile across a wide range of doses. Patients who have a history of renal insufficiency or kidney stones appear to be at an increased risk of forming new kidney stones (28,29). In some studies, ingestion of high dose vitamin C resulted in increased markers of oxidative stress (30). We thus assign a TOE "Risks" grade of B (Table 1).

At an oral dose of 2,000 mg daily, vitamin C can be purchased for less than $10 per month (31).

Conclusion

Vitamin C is safe and inexpensive. As an antioxidant, it has a plausible mechanism for influencing the course of neurodegenerative diseases. Two flawed preclinical studies by the same group showed benefits in a mouse model of familial ALS. There are two case reports in which it was associated with improvement. However, there are multiple possible explanations for the improvement in these cases. It is not clear which if any dose of vitamin C might be beneficial for PALS; a small clinical trial using oral vitamin C at 2,000 mg daily was unable to demonstrate benefits in PALS. Based on this negative trial, we currently advise against using vitamin C to treat ALS.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding

ALSUntangled is sponsored by the ALS Association. Richard Bedlack has research support from ALSA, Orion, MediciNova, and the Healey Center, and consulting support from AB Science, Alexion, ALSA, Amylyx, Biogen, Brainstorm Cell, Corcept, GenieUs, Guidepoint, ITF Pharma, Mallinkrodt, New Biotic, Orphazyme, and Woolsey Pharma.

ORCID

Christopher Mcdermott http://orcid.org/0000-0002-1269-9053
Paul Wicks http://orcid.org/0000-0002-2293-9284

References

1. ALSUntangled [online]. Available at: https://www.alsuntangled.com/future-reviews/. Accessed April 22, 2021.
2. Carr A, Maggini S. Vitamin C and immune function. Nutrients. 2017;9:1211.
3. Kocot J, Luchowska-Kocot D, Kielczykowska M, Musik I, Kurzepa J. Does vitamin C influence neurodegenerative disease and psychiatric disorders? Nutrients. 2017;9:659.
4. Schleicher R, Carroll M, Ford E, Lacher D. Serum vitamin C and the prevalence of vitamin C deficiency in the United States 2003-2004 National Health and Nutrition Examination Survey (NHANES). Am J Clin Nutr. 2009;90:1252–63.
5. US Centers for Disease Control and Prevention. Second national report on biochemical indicators of diet and nutrition in the US population 2012. Atlanta GA USA: National Center for Environmental Health; 2012.
6. Johnston CS, Barkyoumb G, Schumacher S. Vitamin C supplementation slightly improves physical activity levels and reduces cold incidence in men with marginal vitamin C status: a randomized controlled trial. Nutrients. 2014;6:2572–83.
7. Plevin D, Galletly C. The neuropsychiatric effects of vitamin C deficiency: a systematic review. BMC Psychiatry. 2020;20:315.
8. Wang M, Liu Z, Sun W, Yuan Y, Jiao B, Zhang X, et al. Association between vitamins and amyotrophic lateral sclerosis: a center-based survey in mainland China. Front Neurol. 2020;11:488.
9. Blasco H, Corcia P, Moreau C, Veau S, Fournier C, Vourc'h P, et al. 1H-NMR-based metabolomic profiling of CSF in early amyotrophic lateral sclerosis. PLOS One. 2010;5:e13223.
10. Fitzgerald KC, O'Reilly ÉJ, Fondell E, Falcone GJ, McCullough ML, Park Y, et. al. Intakes of vitamin C and carotenoids and risk of amyotrophic lateral sclerosis: pooled results from 5 cohort studies. Ann Neurol. 2013;73:236–45.
11. Prell T, Grosskreutz J, the Pooled Resource Open-Access ALS Clinical Trials Consortium. Use of vitamins by participants in amyotrophic lateral sclerosis clinical trials. PLOS One. 2020;15:e0237175.
12. Hemerkova P, Valis M. Role of oxidative stress in the pathogenesis of amyotrophic lateral sclerosis: antioxidant metalloenzymes and therapeutic strategies. Biomolecules. 2021;16:437.
13. Dragstead L. Biomarkers of exposure to vitamins A, C and E and their relation to lipid and protein oxidation markers. Eur J Nutrition 2008;47:3.
14. Block G, Jensen C, Morrow J, Holland N, Norkus E, Milne G, et al. The effect of vitamins C and E on biomarkers of oxidative stress depends on baseline level. Free Radic Biol Med. 2008;45:377–84.
15. Przedborski S, Donaldson D, Murphy P, Hirsch O, Lange D, Naini A, et. al. Blood superoxide dismutase, catalase and glutathione peroxidase activities in familial and sporadic amyotrophic lateral sclerosis. Neurodegeneration. 1996;5:57–64.
16. Covarrubias-Pinto A, Acuna A, Beltran F, Torres-Diaz L, Castro M. Old things new view: ascorbic acid protects the brain in neurodegenerative disorders. Int J Mol Sci. 2015;16:28194–217.
17. Galasko D, Peskind E, Clark C, Quinn J, Ringman J, Jicha G, Alzheimer's Disease Cooperative Study, et al. Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures. Arch Neurol. 2012;69:836–41.
18. The ALSUntangled Group. ALSUntangled: introducing the table of evidence. Amyotroph Lateral Scler Frontotemporal Degen 2015;16:142–5.
19. Nagano S, Ogawa Y, Yanagihara T, Sakoda S. Benefit of a combined treatment with trientine and ascorbate in familial amyotrophic lateral sclerosis model mice. Neurosci Lett. 1999;265:159–62.
20. Nagano S, Fujii Y, Yamamoto T, Taniyama M, Fukada K, Yanagihara T, et al. The efficacy of trientine or ascorbate alone compared to that of the combined treatment with these two agents in familial amyotrophic lateral sclerosis model mice. Exp Neurol. 2003;179:176–80.
21. PatientsLikeMe [online]. Available at: https://www.patientslikeme.com/treatment/vitamin-c-ascorbic-acid?-brand=false. Accessed April 20, 2021.
22. ALS Reversals [online]. Available at http://www.alsreversals.com. Accessed April 30 2021.
23. Harrison D, Mehta P, Van Es M, Stommel E, Drory V, Nefussy B, Pooled Resource Open-Access ALS Clinical Trials Consortium, et. al. "ALS reversals": demographics, disease characteristics, treatments, and co-morbidities. Amyotroph Lateral Scler Frontotemporal Degener. 2018;19:495–9.

24. Ellis T, Cudkowicz ME, McKenna-Yasek D, Eggelston PM, Brown RH, Cros D. Combination antioxidant therapy in amyotrophic lateral sclerosis. Neurology. 1997;48:A127.
25. Orrell RW, Lane RJM, Ross M. Antioxidant treatment for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database of Systematic Reviews. 2005;1: CD002829.
26. NIH office of dietary supplements [online]. Available at: https://ods.od.nih.gov/factsheets/VitaminC-Consumer/. Accessed April 20, 2021.
27. Goldfarb A, Patrick S, Bryer S, You T. Vitamin C supplementation affects oxidative stress response to a 30-minute run at 75% V02max. International Journal of Sport Nutrition and Exercise Metabolism. 2005;15: 279–90.
28. Rivers J. Safety of high-level vitamin C ingestion. Int J Vitamin Nutr Res Suppl. 1989;30:95–102.
29. Nauman G, Gray J, Parkinson R, Levine M, Paller C. Systematic review of intravenous ascorbate in cancer clinical trials. Antioxidants. 2018;7:89.
30. Pérez-Torres I, Guarner-Lans V, Rubio-Ruiz ME. Reductive stress in inflammation-associated diseases and the pro-oxidant effect of antioxidant agents. IJMS. 2017; 18:2098.
31. Amazon [online]. Available at: https://www.amazon.com/s?k=vitamin+c&ref=nb_sb_noss_2. Accessed May 3, 2021.