CASE REPORT

Parenteral vitamin C relieves chronic fatigue and pain in a patient with rheumatoid arthritis and mononeuritis multiplex secondary to CNS vasculitis

Anitra C. Carr[1], Margreet C.M. Vissers[1], John S. Cook[2]

1. Department of Pathology, University of Otago, Christchurch, New Zealand; 2. New Brighton Health Care, New Brighton, Christchurch, New Zealand.

Correspondence: Anitra C. Carr. Address: Department of Pathology, University of Otago, Christchurch, New Zealand. Email: anitra.carr@otago.ac.nz

Received: November 15, 2014 **Accepted:** January 6, 2015 **Online Published:** January 12, 2015
DOI: 10.5430/crcp.v2n2p57 **URL:** http://dx.doi.org/10.5430/crcp.v2n2p57

Abstract

Preliminary studies have shown parenteral vitamin C to be effective against cancer-related fatigue and herpes zoster-related pain. Our aim was to determine the effects of parenteral vitamin C on chronic fatigue and pain in a patient with multiple morbidities. Here we report on a case of a 47 year old female with rheumatoid arthritis and mononeuritis multiplex, secondary to CNS vasculitis, whose primary symptoms were chronic fatigue, pain and insomnia. Parenteral vitamin C (50 g/session) was administered to this patient and quality of life (EORTC QLQ-C30) and multidimensional fatigue (MFSI-SF) questionnaires were administered before and after treatment. The quality of life questionnaire showed a dramatic improvement in the patient's global health status, in particular, enhanced physical, role and cognitive functioning. Most notably, dramatic decreases were observed in the patient's primary symptoms of fatigue, pain and insomnia. The multidimensional fatigue questionnaire indicated decreases in general, physical, emotional and mental fatigue, as well as a doubling of vigour. No adverse events were reported by the patient or her physician following parenteral vitamin C administration. The use of parenteral vitamin C could be considered for the management of chronic fatigue and pain.

Key words

Vitamin C, Chronic fatigue, Pain, Quality of life, Rheumatoid arthritis, Vasculitis

1 Introduction

Parenteral vitamin C has been administered by physicians for many decades, primarily as an alternative therapy for cancer and viral infections [1]. Patients typically receive doses of ~28 g vitamin C per treatment, on average once every four days [1]. We and others have shown that parenteral vitamin C is an effective therapy for cancer- and chemotherapy-related fatigue [2]. A number of case reports and small clinical studies have also shown that parenteral vitamin C (doses of 2.5 g to 15 g per treatment) can rapidly decrease herpes zoster-associated pain [3, 4]. Vitamin C has known antioxidant, anti-inflammatory and neurological co-factor activities which may contribute to its anti-fatigue and analgesic effects [5, 6]. Here we present the case of a 47 year old female with rheumatoid arthritis and mononeuritis multiplex, secondary to CNS vasculitis, the latter possibly resulting from multiple drug reactions to treatments for hepatitis C and rheumatoid arthritis.

Parenteral vitamin C was administered to determine if this could relieve her primary symptoms of chronic fatigue, pain and insomnia. Due to the debilitating nature of chronic fatigue and pain, any therapy that can alleviate these symptoms will significantly improve the quality of life of sufferers.

2 Case history

Hepatitis C infection. The patient, a 47 year old female, contracted hepatitis C (genotype 1) in 1999, likely from blood transfusion during childbirth. In 2008 hepatitis C antibodies were present with a viral load of 21,389 IU/ml, increasing to 163,829 IU/ml early 2009. The patient commenced a 48 week course of antiviral therapy with Ribavirin; side effects including fatigue and peripheral paraesthesiae were noted. The patient also presented with stress, depressive symptoms and some suicidal thoughts, and was prescribed Doxepin for depression. In mid-2009 the patient commenced treatment with pegylated interferon-alpha. Side-effects to this included loss of sensation along left foot, calf and hand, numb fingers and pain in arm, as well as neurological decline shortly after interferon therapy, which is also known to cause fatigue [7].

Rheumatoid arthritis. From mid-2008 the patient presented with inflammatory polyarthritis (positive rheumatoid factor and anti-CCP, symptoms of achy joints, chest pain, bilateral shoulder discomfort, swelling of wrists and pain in knees, TMJs, cervical spine). Chronic hepatitis C infection was likely a significant driver for the rheumatoid arthritis [8]. She was prescribed the corticosteroid Prednisone, the NSAID Diclofenac SR (had reacted to Meloxicam), Omeprazole to protect stomach, Voltaren, codeine phosphate, and Codalgin for pain. From 2009 she was also prescribed calcium carbonate and cholecalciferol to protect bones, and the antifolate drug Co-trimoxazole. Codalgin was recorded as having no effect on pain. In early 2011, the patient experienced further deterioration in mobility and in early 2012 rheumatoid arthritis was still active, with concomitant insomnia and feelings of exhaustion.

From mid-2012 the patient trialled a number of disease modifying anti-rheumatic drugs (DMARDs), including the anti-folate drug Methotrexate, which caused nausea and vomiting after one dose. She then commenced with Leflunomide; however, suffered nausea, headaches, light-headedness and numbness. Therefore she was prescribed Sulphasalazine, which was ineffective. In early 2013 she received anti-TNF drug Adalimumab (Humira), but she presented with a possible drug reaction, *i.e.* erythematous maculopapular rash over entire legs, arms and back (prescribed antihistamine Cetrizine). In mid-2013 the patient commenced with anti-TNF drug Etanercept, to which she also reacted, developing a rash, so this was also discontinued.

Mononeuritis multiplex. In mid-2010 the patient was diagnosed with mononeuritis multiplex, secondary to CNS vasculitis, as determined by MRI indicating multiple areas of white matter change, possibly resulting from multiple drug reactions to treatments for hepatitis C and rheumatoid arthritis. She began iv Cyclophosphamide infusions (8 cycles) and was prescribed Ondansetron and Metoclopramide 48 hr following iv Cyclophosphamide for nausea.

Co-morbidities. In 2002 the patient contracted Type II herpes simplex meningitis which required hospitilisation (prescribed Acyclovir and iv Ceftriaxone). Again in 2012 she presented with herpes simplex infection (prescribed Aciclovir). In early 2009 the patient exhibited low haemoglobin suggestive of iron deficiency (possibly due to Diclofenac). In 2009 the patient also developed hypertension and was prescribed Felodipine and Cilazapril, then Bendrofluazide and Enalapril maleate. The patient also experienced chronic insomnia (possibly due to Prednisone), anxiety and unsteady gait and was prescribed Lorazapam as required for anxiety and insomnia and Nortiptyline for sleep. At the time of the case study (late 2013), she was experiencing a respiratory tract infection (prescribed Flucloxacillin and Roxithromycin).

Vitamin C therapy. Parenteral vitamin C was recommended by the patient's physician late 2013, in addition to prescribed medications, to determine if this would improve her lethargy. The patient was assessed for standard contraindications: haemochromatosis, renal dysfunction or history of kidney stones and glucose-6-phophate dehydrogenase gene deficiency,

and signed an informed intravenous vitamin C consent form which outlined possible side-effects. A trial dose of 12 g vitamin C (AscorL500, McCuff Pharmaceuticals, Sanata Ana, USA) was administered with no issues observed, and a total dose of 50 g was subsequently administered in 100 ml of normal saline by drip infusion over a 30 minute period. This was repeated on two other occasions about one week apart. A standard operating procedure was followed at each appointment, including assessment of blood pressure, heart rate, temperature, phlebitis/tissuing, and any discomfort. The patient was advised to notify the GP of any concerns or if feeling unwell and follow-up blood test monitoring of kidney function was carried out as part of treatment review.

The European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) [9] and the Multidimensional Fatigue Symptomology Inventory questionnaire (MFSI-SF) [10] were administered approximately one month apart, before treatment commenced and two days after the third parenteral vitamin C injection. Although the patient did not have cancer, she was experiencing similar symptoms following chemotherapy as cancer patients undergoing chemotherapy [2], thus the EORTCQLQ-C30 was felt to be appropriate to use in her case.

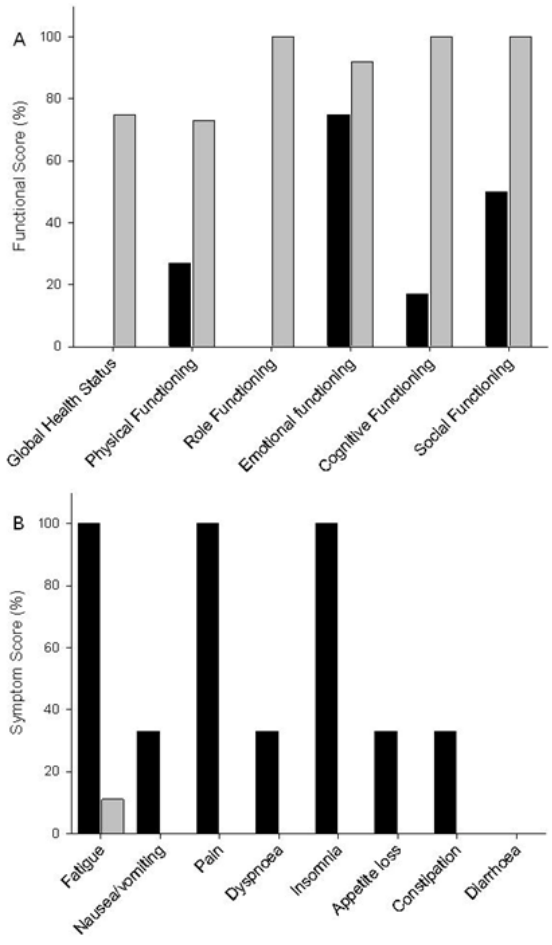

Figure 1. Patient's health-related quality of life scores before (black bars) and after (grey bars) i.v. vitamin C administration. All of the scales range in score from 0 (no bar) to 100, with a high score representing a higher response level, *i.e.* a high score for the global health status scale (A) represents a high quality of life, and a high score for a functional scale (A) represents a high/healthy level of functioning, whereas a high score for a symptom scale (B) represents a high level of symptomology/problems.

The quality of life questionnaire showed a dramatic improvement in the patient's global health status, and in particular, enhanced physical, role and cognitive functioning (see Figure 1A). Most notably, dramatic decreases were observed in the patient's primary symptoms of fatigue, pain and insomnia (see Figure 1B). According to the patient, the decrease in symptoms was observed within 12 hours and lasted for 48 hours following each treatment. Since fatigue can express on physical, emotional and mental levels, a questionnaire that covers the multidimensional aspects of fatigue was also used [10]. This indicated decreases in general, physical, emotional and mental fatigue, as well as a doubling of vigour (see Figure 2). Interestingly, the patient also reported a rapid cessation of the symptoms of her current respiratory tract infection. No adverse events were reported by the patient or her physician following parenteral vitamin C administration.

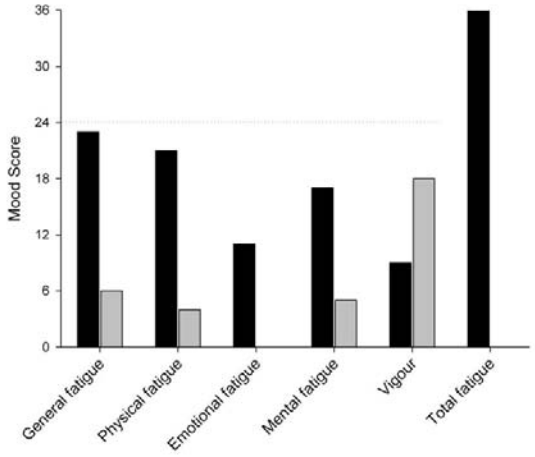

Figure 2. Patient's multidimensional fatigue scores before (black bars) and after (grey bars) i.v. vitamin C administration. All of the single-item measures range in score from 0 (not at all = no bar) to 24 (extremely). Total fatigue represents the sum of general, physical, emotional and mental fatigue scores minus the vigour score.

3 Discussion

This case indicates that parenteral vitamin C (50 g/treatment) can alleviate the symptoms of chronic fatigue, pain and insomnia for approximately two days following each treatment, with no adverse side effects observed. Vitamin C is a potent antioxidant and acts as a cofactor for numerous biosynthetic and regulatory enzymes in the body [5], which may account for its observed effects in this case. Oxidative stress has been implicated in chronic fatigue syndrome [11] and chemotherapy-related fatigue [12]. Parenteral vitamin C has been shown to decrease both cancer - and chemotherapy - related fatigue in cancer patients [2]. Fatigue is common in patients with chronic hepatitis C infection and is exacerbated with interferon-alpha treatment [7, 13]. Interestingly, trials have shown that L-carnitine can alleviate the interferon-alpha-dependent fatigue in these patients [14]. Since vitamin C acts as a cofactor for the biosynthesis of carnitine, a compound required for the generation of metabolic energy [15], this may indicate a plausible mechanism by which the vitamin alleviates physical fatigue.

Vitamin C also acts as a cofactor for the biosynthesis of the neurotransmitters norepinephrine, dopamine and serotonin [16], as well as neuropeptide hormones, such as mood enhancing oxytocin [17]. Depression is often associated with fatigue and is common in Hepatitis C patients receiving interferon-alpha treatment [7]. Interestingly, depression is an early symptom of vitamin C depletion [18] and although our patient did not exhibit overt signs of depression, we and others have observed decreased depression in hypovitaminosis C individuals following supplementation with vitamin C [18, 19]. Parenteral vitamin C also readily and rapidly reduces pain in patients with shingles [3, 4], likely through its neuromodulatory functions [20]. Recent studies have shown that high dose oral vitamin C acts as an analgesic for complex regional pain syndrome [21], however, the patient reported no effects on her pain levels whilst consuming 1,000 mg/d oral vitamin C. Placebo injections were not carried out with this case, thus it is not possible to rule out a placebo effect. Nevertheless, it is likely that, due to the multiple *in vivo* functions of vitamin C, the parenteral vitamin C contributed to the observed reduction of fatigue and pain in this patient.

Despite its debilitating nature, fatigue is often overlooked and seldom treated [22]. Treatments such as central nervous system stimulants are often ineffective and have adverse side effects [23]. Our data indicates that parenteral vitamin C could be considered for the safe and effective management of chronic fatigue and pain.

References

[1] Padayatty SJ, Sun AY, Chen Q, *et al*. Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. PLoS One. 2010; 5(7): e11414. PMid: 20628650. http://dx.doi.org/10.1371/journal.pone.0011414

[2] Carr AC, Vissers MCM, Cook JS. The effect of intravenous vitamin C on cancer- and chemotherapy-related fatigue and quality of life. Front Oncol. 2014; 4(283): 1-7.
[3] Schencking M, Vollbracht C, Weiss G, *et al*. Intravenous vitamin C in the treatment of shingles: results of a multicenter prospective cohort study. Med Sci Monit. 2012; 18(4): CR215-24. PMid: 22460093. http://dx.doi.org/10.12659/MSM.882621
[4] Chen JY, Chang CY, Feng PH, *et al*. Plasma vitamin C is lower in postherpetic neuralgia patients and administration of vitamin C reduces spontaneous pain but not brush-evoked pain. Clin J Pain. 2009; 25(7): 562-9. PMid: 19692796. http://dx.doi.org/10.1097/AJP.0b013e318193cf32
[5] Du J, Cullen JJ, Buettner GR. Ascorbic acid: Chemistry, biology and the treatment of cancer. Biochim Biophys Acta. 2012; 1826(2): 443-57. PMid: 22728050.
[6] Mikirova N, Casciari J, Rogers A, *et al*. Effect of high-dose intravenous vitamin C on inflammation in cancer patients. J Transl Med. 2012; 10: 189. PMid: 22963460. http://dx.doi.org/10.1186/1479-5876-10-189
[7] Majer M, Welberg LA, Capuron L, *et al*. IFN-alpha-induced motor slowing is associated with increased depression and fatigue in patients with chronic hepatitis C. Brain Behav Immun. 2008; 22(6): 870-80. PMid: 18258414. http://dx.doi.org/10.1016/j.bbi.2007.12.009
[8] Calvaruso V, Craxi A. Immunological alterations in hepatitis C virus infection. World J Gastroenterol. 2013; 19(47): 8916-23. PMid: 24379616. http://dx.doi.org/10.3748/wjg.v19.i47.8916
[9] Aaronson NK, Ahmedzai S, Bergman B, *et al*. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993; 85(5): 365-76. PMid: 8433390. http://dx.doi.org/10.1093/jnci/85.5.365
[10] Stein KD, Martin SC, Hann DM, *et al*. A multidimensional measure of fatigue for use with cancer patients. Cancer Pract. 1998; 6(3): 143-52. PMid: 9652245. http://dx.doi.org/10.1046/j.1523-5394.1998.006003143.x
[11] Richards RS, Roberts TK, McGregor NR, *et al*. Blood parameters indicative of oxidative stress are associated with symptom expression in chronic fatigue syndrome. Redox Rep. 2000; 5(1): 35-41. PMid: 10905542. http://dx.doi.org/10.1179/rer.2000.5.1.35
[12] Gilliam LA, St Clair DK. Chemotherapy-induced weakness and fatigue in skeletal muscle: the role of oxidative stress. Antioxid Redox Signal. 2011; 15(9): 2543-63. PMid: 21457105. http://dx.doi.org/10.1089/ars.2011.3965
[13] Seaman K, Paterson BL, Vallis M, *et al*. Future directions for investigation of fatigue in chronic hepatitis C viral infection. Chronic Illn. 2009; 5(2): 115-28. PMid: 19474234. http://dx.doi.org/10.1177/1742395309104476
[14] Malaguarnera M, Vacante M, Bertino G, *et al*. The supplementation of acetyl-L-carnitine decreases fatigue and increases quality of life in patients with hepatitis C treated with pegylated interferon-alpha 2b plus ribavirin. J Interferon Cytokine Res. 2011; 31(9): 653-9. PMid: 21923249. http://dx.doi.org/10.1089/jir.2011.0010
[15] Rebouche CJ. Ascorbic acid and carnitine biosynthesis. Am J Clin Nutr. 1991; 54(6 Suppl): 1147S-52S. PMid: 1962562.
[16] May JM, Qu ZC, Meredith ME. Mechanisms of ascorbic acid stimulation of norepinephrine synthesis in neuronal cells. Biochem Biophys Res Commun. 2012; 426(1): 148-52. PMid: 22925890. http://dx.doi.org/10.1016/j.bbrc.2012.08.054
[17] Englard S, Seifter S. The biochemical functions of ascorbic acid. Annu Rev Nutr. 1986; 6: 365-406. PMid: 3015170. http://dx.doi.org/10.1146/annurev.nu.06.070186.002053
[18] Levine M, Conry-Cantilena C, Wang Y, *et al*. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. Proc Natl Acad Sci U S A. 1996; 93(8): 3704-9. PMid: 8623000. http://dx.doi.org/10.1073/pnas.93.8.3704
[19] Carr AC, Vissers MCM. Good nutrition matters: hypovitaminosis C associated with depressed mood and poor wound healing. NZ Med J. 2012; 125(1362): 107-9. PMid: 23178613.
[20] Harrison FE, May JM. Vitamin C function in the brain: vital role of the ascorbate transporter SVCT2. Free Radic Biol Med. 2009; 46(6): 719-30. PMid: 19162177. http://dx.doi.org/10.1016/j.freeradbiomed.2008.12.018
[21] Shibuya N, Humphers JM, Agarwal MR, *et al*. Efficacy and safety of high-dose vitamin C on complex regional pain syndrome in extremity trauma and surgery--systematic review and meta-analysis. J Foot Ankle Surg. 2013; 52(1): 62-6. PMid: 22985495. http://dx.doi.org/10.1053/j.jfas.2012.08.003
[22] Vogelzang NJ, Breitbart W, Cella D, *et al*. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. The Fatigue Coalition. Semin Hematol. 1997; 34(3 Suppl 2): 4-12. PMid: 9253778.
[23] Ruddy KJ, Barton D, Loprinzi CL. Laying to rest psychostimulants for cancer-related fatigue? J Clin Oncol. 2014; 32(18): 1865-7. PMid: 24799492. http://dx.doi.org/10.1200/JCO.2014.55.8353