Vitamin C Improves Healing of Foot Ulcers; A Randomised, Double-Blind, Placebo-Controlled Trial

Running Title: Vitamin C Improves Healing of Foot Ulcers

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Abstract

Chronic foot ulcers are associated with a high risk of osteomyelitis, poor quality of life, amputations and disability. Few strategies improve their healing, and amputation rates in high-risk foot services are usually over 30%.

We conducted a randomised, inactive-placebo controlled, double-blind trial of 500mg of slow-release vitamin C in 16 people with foot ulcers conducted in the foot-wound clinic at Westmead Hospital. Nine were randomised to control and 7 to vitamin C. When serum vitamin C results become available at 4 weeks, all people with deficiency were offered both vitamin C and glucosamine tablets for the next 4 weeks. Patients without baseline deficiency continued their original assigned treatment.

The primary outcome was percent ulcer healing (reduction in ulcer size) at 8 weeks. Fifty percent of subjects had baseline vitamin C deficiency, half having undetectable levels. Healing at 8 weeks was significantly better in the vitamin C group (median 100% versus –14%, p=0.041). Healing without amputation occurred in all patients in the vitamin C group. In contrast, 44% of controls had not healed their ulcer at the end of the study period.

Vitamin C improved healing of foot ulcers. Further studies are needed to determine whether there is a threshold effect for serum vitamin C above which therapy is ineffective and whether there are better or lesser responding subgroups. Because of its low cost and ease of access and administration we recommend offering vitamin C therapy to all people who have chronic foot ulcers and potentially suboptimal vitamin C intake.

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Trial registration number: ACTRN12617001142325

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Scurvy is the clinical manifestation of severe vitamin C deficiency. Hippocrates (460 BC–370 BC) described scurvy in the ancient Greek army in men with leg pain, and bleeding gums with gangrene \(^{(1)}\). It is estimated that more than 2 million sailors died of scurvy between 1500 and 1800 AD, with common final causes of death including infection, bleeding and fractures.

Lind’s treatise on scurvy in 1753 described treating 6 pairs (12 subjects) with potential remedies. Five pairs were given treatment with vinegar, cider, elixir of vitriol, mustard and garlic purges, or drinking 2 pints of seawater daily. These 5 treatments were ineffective. One pair received oranges and lemons and only these 2 subjects recovered \(^{(2)}\). Vitamin C itself was not discovered until 1933 and Albert von Szent-Györgyi received the 1937 Nobel prize for this and other work.

In current times, vitamin C deficiency and scurvy are usually presumed to be rare in the absence of famine or eating disorders. However, we reported a case series of people with diabetes and poorly healing lower limb ulcers \(^{(3)}\) in whom there was prompt ulcer healing with vitamin C replacement. A report published during the period in which our study was conducted identified a 59% rate of vitamin C deficiency in a high-risk foot ulcer clinic \(^{(4)}\).

Foot ulceration can be defined as erosion of tissue or a breach in skin below the ankle. Conditions that increase the risk of foot ulceration include diabetes, peripheral vascular disease, any disease associated with sensory peripheral neuropathy, and conditions affecting foot structure or architecture. Foot deformity, past foot ulcers and amputation are the most significant risk factors for future ulcers \(^{(5)}\). These ulcers are often complicated by infection, including osteomyelitis, and/or impaired blood supply (vascular disease). Chronic foot ulcers carry a high risk of amputation.

Vitamin C is required for collagen formation, and for proper function of the immune system to decrease and control infections. We hypothesised that vitamin C may improve foot ulcer
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healing, and tested this with a randomised, double-blind, glucosamine-placebo-controlled trial of vitamin C supplementation in people attending the High-Risk Foot Clinic (now called Foot Wound Clinic) at a tertiary referral hospital.

METHODS

This was a pragmatic, investigator-initiated, randomised, double-blind, inactive-placebo-controlled trial. No commercial support was provided for the trial, which was funded by a grant from the Research and Education Network of Westmead Hospital. Ethics approval was given by the Human Research Ethics Committee (HREC) of Western Sydney Local Health District (WSLHD).

Patients

People were eligible to participate if they were adults who presented as a new patient to the High-Risk Foot Clinic at Westmead Hospital and had a current foot ulcer. No patients required exclusion for healing between booking their first clinic visit and attending. Other exclusion criteria were inability to give informed consent for cognitive issues (n=3 excluded) or language issues (0), and a decision being made at that first visit that the subject would proceed to amputation (n=1). One additional patient was excluded because their serum vitamin C level had been measured before clinic presentation and they were already being treated with vitamin C supplements. Two patients declined to consent after learning that a blood test was involved. Patient flow is detailed in the Consort Diagram (Figure 3).

After signing informed consent, subjects completed a brief dietary survey and underwent a venipuncture for measurement of serum vitamin C. They were then randomised to vitamin C, 500 mg daily in a slow-release capsule, or the inactive comparator which was identical-appearing glucosamine sulfate capsules (1000mg). The vitamin C was a commercial product made by Blackmores purchased from the local pharmacy. The slow-release formulation was
chosen because it is safer in people with renal impairment, giving lower risk of oxaluria and also, because it isn’t flavoured / chewable as most vitamin C formulations are, it was easier to obtain a matching appearing control. Glucosamine was a commercial product made by BioOrganics also purchased from the local pharmacy. Neither Blackmores nor BioOrganics had any role in the trial design, funding, analysis or preparation of this report. These medications were delivered to the trials-pharmacy at Westmead Hospital for dispensing.

Patients were recruited from January 2018 to March 2019. Numbers of subjects were estimated using PowerStat (Vanderbilt), α 0.05, power 0.8, assuming a 25% standard deviation in ulcer healing and a 40% improvement in ulcer size with vitamin C. This recommended 7 patients per group. The trial was stopped at 16 subjects.

**Randomisation and treatment**

Randomisation was carried out by computerised random number generation (Excel) and the clinical trials pharmacists dispensed 4 weeks of the assigned medication. Patients were instructed to take 1 tablet daily, and continue normal clinical attendance and all usual care as determined by the High-Risk Foot Clinic Team. Only the clinic trials pharmacist had access to the treatment assignment information, all other staff and patients were blinded.

At our institution, the serum vitamin C result takes approximately 4 weeks to return. The vitamin C result was available to the treating team in the clinic from that time. When the first 28 days of medication were completed, if the patient was vitamin C deficient, they were dispensed both vitamin C and glucosamine tablets by the clinical trials pharmacist for the second 28 days. If the baseline serum vitamin C was normal, they continued their original medication for a further 28 days. This was done so that all deficient people were offered treatment with vitamin C while original treatment assignment remained blinded. As stated
above, all other care was provided as ‘usual care’ at the clinic; there were no other study-interventions.

Outcome measures

The primary endpoint of the study was percent ulcer healing at 8 weeks (percent reduction compared to initial ulcer volume). Ulcer size was estimated using a silhouette 3D camera, or if unavailable (e.g. at home visits), by measuring ulcer dimensions. Ulcers were presumed to be ‘punched out’ at uniform depth for this purpose. If ulcers became larger, percent ulcer healing was negative. The closest visit to 8 weeks was used for the primary endpoint. This occurred at a median of 63 days for the glucosamine group and 55 days for the vitamin C group. This time point was chosen based on clinic experience and data indicating that early heal is a good predictor of final healing (20, 21). People who underwent amputations before 8 weeks (N=2) had the ulcer size at the date of amputation used for their 8-week value for the primary endpoint.

Complete ulcer healing was considered to have occurred when the epithelium was intact (i.e. 100% healing with no ongoing drainage). People who underwent amputations were considered to not have healed ulcers. Secondary outcomes included time to 50% ulcer healing, time to complete ulcer healing and rate of healing of ulcers. Data was collected for amputation rates, which were a prespecified secondary outcome although when we planned the study, we considered that it was not powered to assess this outcome.

Serum vitamin C measurement

The blood test request forms included instructions to wrap samples in foil and place on ice immediately. Serum vitamin C was measured following precipitation of proteins, followed by separation on a reverse-phase HPLC column (lab-packed LiChrosorb RP-18 (5 micron) 150 x 3.0mm) and measurement using an amperometric (BAS) electrochemical detector. Intra-
assay CV at a vitamin C level of 45μmol/L is 6.9% and at 87μmol/L is 6.5%. The detection limit is 5μmol/L, and the assay is linear to at least 200μmol/L. Normal range is 40-100μmol/L. People with undetectable levels returned a result of <5μmol/L and 4μmol/L was used for analysis.

Statistical analysis

SPSS version 21 or GraphPad Prism version 8 were used for analysis. Analysis was by intention to treat. Where people had amputations, their ulcer was considered to not have healed and the ulcer size prior to amputation was used. Where values were not normally distributed (e.g. percent ulcer healing) as indicated by skewness values >1 (calculated in SPSS), non-parametric testing was used. Two tailed p-values were used. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographic and baseline characteristics of the trial subjects are shown in Table 1. Nine people were randomised to control and 7 to vitamin C. Four subjects in each group had known vascular disease, and 4 subjects in each group had diabetes mellitus. All subjects had at least one of vascular disease, diabetes, neuropathy or deformed foot architecture. There was a wide age-range, with the younger adult patients (18-44, N=3) all having long-standing type 1 diabetes.

Baseline ulcer size was non-significantly larger in the people assigned to vitamin C, and was not normally distributed (Figure 1A, note log-scale for y-axis). Baseline vitamin C levels were not measured in 2 people as they did not attend the venipuncture service after consenting to participate in the study, and being randomised (1 control, 1 vitamin C) and having medications dispensed. They were considered to be vitamin C sufficient for intention-to-treat purposes. Median vitamin C in the study population was 30.5 μmol/L (interquartile range 4-52). Eight of the 16 subjects were vitamin C deficient, with 4 subjects having
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undetectable levels (Figure 1B). Four people in each treatment group had baseline deficiency. The shaded grey box indicates the normal range.

The primary endpoint, as pre-specified in the clinical trial registry, was percent ulcer healing at 8 weeks (percentage reduction in ulcer volume). This was significantly better in people in the vitamin C group at median 100% compared to −14% in the glucosamine group (p=0.041, Figure 1C, yellow-filled symbols indicate people who were deficient at baseline). Median time to 50% ulcer healing was significantly faster in the vitamin C group at a median of 20 days compared to a median of 48 days in the 5 of 9 subjects who achieved 50% ulcer healing in the glucosamine group (Figure 1D, p=0.028).

Kaplan-Meier analysis of 50% healing showed significantly improved results in the vitamin C group (Figure 2A, p=0.004, deficient-at-baseline subjects have yellow symbols).

All 7 vitamin C subjects went on to complete ulcer healing at a median of 77 days (range 21 to 190 days), Figure 2B. Five of 9 subjects in the glucosamine group went on to complete ulcer healing at a median of 77 days (range 26 to 146 days).

Serum vitamin C was positively correlated with serves of cooked vegetables eaten per day (r=0.558, p<0.05). Unexpectedly, neither reported fruit nor fruit juice intake correlated with vitamin C. As expected, meat, fish, nut and water consumption did not correlate with vitamin C. Baseline ulcer size was negatively correlated with baseline serum vitamin C (r= -0.622, p<0.05 by Spearman testing). In the whole group, ulcer size at first and second follow-up visits also correlated negatively with vitamin C (r= -0.656, and -0.754 respectively, both p<0.05). The relationship between follow-up ulcer size and baseline vitamin C disappeared in the vitamin C group but strengthened in the glucosamine group (r= -0.735 (p<0.05), and -0.927 (p<0.01), respectively).
Guidelines in Australia for treatment of diabetes-related foot complications are overdue for review \(^{(11)}\). Similar guidelines for people without diabetes are not available but overall the European Wound Management Association (EWMA) guidelines describe wound care and the International Working Group on the Diabetic Foot (IWGDF) guidelines describe prevention, assessment and interventions. In general, people without diabetes are treated similarly.

Management for both groups includes pressure off-loading (removing physical pressure from the wound) which speeds wound healing \(^{(12)}\) and protects from further injury. For people with no contraindications (such as impaired vascular supply or active infection), this should be in the form of a non-removable, full-contact individualised boot or cast. Appropriate, removable footwear should be used for people with vascular compromise or infection.

For people with impaired vascular supply, improving blood flow when possible assists healing \(^{(11)}\). There is some evidence that hydrogel dressings may assist in selected wounds \(^{(13)}\).

In 2018, a multi-centre randomised controlled trial (RCT) of topical epidermal growth factor spray showed significant benefit in diabetes-related foot ulcers \(^{(14)}\). Ulcers in people without diabetes were not studied.

Most other strategies have not proven beneficial \(^{(13)}\). Many were not tested in RCTs or the results were inconclusive. IWGDF updated their previous review in 2016, and concluded that: “with the possible exception of negative pressure wound therapy in post-operative wounds \(^{(15)}\), there is little published evidence to justify the use of newer therapies. Analysis of the evidence continues to present difficulties in this field as controlled studies remain few and the majority continue to be of poor methodological quality \(^{(13, 16)}\).”

Perhaps surprisingly, there are no trials showing that improved blood glucose control in people with diabetes hastens ulcer healing \(^{(17)}\). Since high blood glucose levels are
detrimental to immune cell function, it is still reasonable to aim for glucose levels < 11 mmol/L (200mg/dL). In addition, *long-term* better glycaemic control decreases the risks of amputations, so this should be the aim for people with foot ulcers because they are at increased risk of amputation \(^{(17)}\).

The remainder of the treatment recommendations are necessarily primarily based on expert opinion and recommend debridement, control of exudate (fluid leak from the wound) and consideration of patient comfort and costs to guide dressing selection \(^{(18,19)}\). The 2019 IWGDF guidelines state on page 164 in relation to wound healing interventions, “*do not use interventions aimed at correcting the nutritional status* (including supplementation of protein, vitamin and trace elements, pharmacotherapy with agents promoting angiogenesis)”.

In the USA, there was a decrease in non-traumatic lower limb amputations in people with diabetes between 2000 and 2009 but this worsened by 50% in the subsequent years to 2015 \(^{(6)}\). It is of particular concern that the increases in amputation rates were greatest in young and middle-aged adults (18–44 and 45–64 years). In 2010, the USA reported rates of amputations in people with diabetes were ~3 times higher than Australia, per head of population \(^{(7)}\). In 2015, there were approximately 115,000 non-traumatic lower limb amputations in the USA in people with diabetes \(^{(6)}\). These figures may be underestimates as minor amputations may be performed in the outpatient setting. In Australia there are approximately 8000 lower limb amputations yearly. Most of these are non-traumatic, below the ankle amputations, and relate to foot ulcers \(^{(8,9)}\). As stated in a ‘call to action’ editorial in the *Medical Journal of Australia*, this is one amputation about every 3 hours \(^{(10)}\).

In this study, vitamin C treatment improved ulcer healing in the high-risk foot clinic subjects. This was a pragmatic trial with few exclusion criteria; patients had to be able to give written informed consent and not be planned for amputation on their first visit. We excluded one
additional person who had pre-clinic testing of their vitamin C, was deficient, and was already taking supplements (Consort diagram, Figure 3). With the intention of making the results as widely applicable as possible, the high-risk foot clinic staff were instructed to continue to give usual standard of care in all other regards. All investigators were blinded to treatment assignment, so all therapeutic decisions were made according to usual care.

Most animals can synthesise vitamin C, but humans, primates, guinea pigs and bats do not have the necessary rate-limiting enzyme. This makes study of scurvy difficult, because animal models are expensive, ethically challenging and / or unfamiliar to most researchers. Data shows improved wound healing in guinea pigs treated with vitamin C (22), but the published human trial data does not answer the question of whether vitamin C is useful for healing foot ulcers.

One randomised controlled trial studied 49 people undergoing elective surgery for tattoo removal. They were supplemented with both vitamin C and pantothenic acid. The trial found no differences in healing (23). However, these people had no reason to expect problems with wound healing. The wounds were clean, electively-created surgical non-foot wounds, rather than injury-related non-healing foot wounds which are the type seen at foot ulcer clinics.

A more relevant model to foot ulcers is pressure sores. A study of 16 people with pressure sores tested 3 treatment groups: 1) control, 2) addition of high protein/energy supplements, and 3) high protein/energy supplements + arginine + vitamin C + zinc supplements daily (24). Group 3 had the fastest ulcer healing. The patient groups all had low baseline zinc levels, so zinc supplementation has a likely benefit which is not possible to separate from vitamin C in this study design. A second randomised controlled trial of 20 surgical patients with pressure sores found significantly improved ulcer healing in the vitamin C group (25). In contrast, a randomised trial of 88 nursing home residents with normal baseline nutrition did not find a
benefit of vitamin C supplementation for pressure ulcers \(^{(26)}\).

A review of the literature for ‘foot ulcer’, ‘randomised or randomised’ and ‘vitamin C or ascorbate or ascorbic’ only identified 2 randomised studies of foot ulcers involving vitamin C. One randomised Iranian study used topical kiwifruit application \(^{(27)}\) and it reported significantly better ulcer healing in the kiwifruit group. Their proposed mechanisms for healing were vitamin C and actinidin, which is a proteolytic agent in kiwifruit. Baseline vitamin C was not reported.

Ulcers in a randomised study of people with leprosy (a relevant model because of the associated neuropathy) were treated with media conditioned with topical amniotic membrane stem cells and supplemented with nothing, vitamin C or vitamin E. There was no control group and all study groups showed significant healing. In both the vitamin C and E groups there was 100% ulcer healing. The vitamin E group healed fastest \(^{(28)}\). This suggests benefits of vitamin C and vitamin E in people with leprosy.

The study presented here appears to be the first report of a randomised controlled trial of vitamin C alone for treatment of foot ulcers.

Synthesis of mature collagen, a critical structural protein in skin-healing, requires vitamin C \(^{(29)}\) which is needed for hydroxylation of the synthesised collagen chains. Appropriate hydroxylation is required for formation of the proper triple-helix structure of mature collagen.

In addition to the need for vitamin C for collagen formation, ascorbic acid is also needed for normal immune function. Osteomyelitis is a common reason for amputations in people with chronic foot ulcers. Inadequate vitamin C nutrition may therefore encourage development of osteomyelitis in the absence of skin integrity. Many of the sailors in centuries past who died from scurvy experienced bone fractures. It is interesting to speculate that lack of vitamin C may further predispose people to osteomyelitis by impairing bone repair.
This study has limitations, especially relating to the small sample size. The consistent results across the study endpoints, biological plausibility and a recent report (4) finding similar rates of vitamin C deficiency in a high-risk foot service increase the likelihood that these results are correct. However, with small numbers, our study could not identify a cut-off point for vitamin C, that is, a level above which supplementation is not beneficial. It was also not able to identify any subgroups who benefited either more or less from supplementation. In addition, the numbers are too few to conduct an economic analysis.

Work on vitamin C trials is unlikely to be funded by industry, due to the low cost and ready availability of this vitamin. These additional studies will probably require larger-scale funding from not-for-profit grant funders, such as NIH or NHMRC.

Vitamin C is cheap, and at 500mg per day of slow-release supplements, it is very safe. If supplementation prevents only one amputation per 10 patients with chronic foot ulcers who would otherwise eventually undergo amputation, treating all patients might prevent more than 10,000 amputations per year in the USA alone. In addition, as time to 50% ulcer healing was significantly shorter in people receiving vitamin C, it is likely that costs of running the service and costs to patients would be lower in people treated with vitamin C.

We recommend consideration of vitamin C supplementation, preferably with a slow-release form, in all people attending for chronic foot ulcers who do not have exemplary dietary fruit and vegetable intake. Ideally, given its very cheap cost to health services, and high likelihood of favourable cost outcomes, this would be provided free to patients, to improve compliance.
Acknowledgements

The authors declare they have no conflicts of interest.

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The study was designed by JEG, CG, LB and VF. Patients were recruited by CG and TL and vascular patients were reviewed by M.V. Data was collected from medical records by TL and JEG. All authors assisted with manuscript preparation and review. The study was approved by the Westmead Human Research Ethics Committee and all participants gave written, informed consent. We would like to thank Ms Olivia Wroth and Dr Andrew Dwyer for proofreading and helpful comments on the paper.
REFERENCES


### Table 1 Baseline characteristics of trial subjects

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Data indicate mean± standard deviation or median (95% confidence interval (CI)). Excess alcohol was considered ≥2 standard drinks per day. Those two people reported consuming ≥4 standard drinks daily. HbA1c is reported for people with known diabetes.
Figure 1. Baseline ulcer and vitamin C, and healing of ulcers. A) Baseline ulcer size. Note log-scale for y-axis. Individual values are shown. Symbols with yellow centers indicate people with vitamin C deficiency. B) Baseline vitamin C levels. The shaded area indicates the normal range. C) Percent healing at 8 weeks (% reduction in ulcer volume). 100% indicates complete healing. Negative values indicate enlarged wounds compared to baseline. Symbols with yellow centers indicate people with baseline vitamin C deficiency. D) Days from baseline visit to 50% reduction in ulcer volume. Symbols with yellow centers indicate people with baseline vitamin C deficiency.
Figure 2. Ulcer healing rates. A) Percent of people with 50% ulcer healing compared to baseline volume (p<0.01). Yellow symbols indicate people with baseline vitamin C deficiency. B) Percent of people with completely healed ulcers. 4 subjects in the control group did not achieve ulcer healing.
Figure 3. Consort diagram.