

# Vitamin C for preventing and treating tetanus (Protocol)

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## ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the effectiveness of vitamin C supplementation for (1) preventing the development of tetanus in vaccinated and unvaccinated individuals and (2) reducing hospital stay and mortality in patients with a diagnosis of tetanus.

## BACKGROUND

'Tetanus' denotes a disease caused by tetanus toxin (tetanospasmin), a protein that is produced by the anaerobic bacterium *Clostridium tetani*. Although the pathological definition of 'tetanus' is based on the specified bacterium and its toxin, the diagnosis is made on a clinical basis. The clinical picture of tetanus is dominated by muscle spasms and rigidity. Often the first sign is the rigidity of the jaw muscles, followed by stiffness of the neck, difficulty in swallowing, and rigidity of abdominal muscles. Other symptoms include elevated temperature, elevated blood pressure, and episodic rapid heart rate. Tetanus may lead to complications such as fractures of the spine or long bones because of contractions and convulsions, and pulmonary embolism, bed sores, and nosocomial infections because of prolonged hospitalization. The current treatment of tetanus consists, for example, of surgical debridement of the wound and antibiotic (metronidazole) to remove the source of infection, tetanus immune globulin to neutralize circulating toxin, and benzodiazepine for sedation and muscle relaxation (Bleck 2005; CDC 2007; Cook 2001; Farrar 2000; Rhee 2005; WHO 2007).

A typical cause of tetanus is a deep penetrating wound where anaerobic bacterial growth may occur, particularly if the wound is contaminated by foreign material such as soil. Vaccination against tetanus has dramatically decreased the incidence of the disease in developed countries, but infrequent cases occur, particularly in elderly people owing to reduced immunoprotection (Gergen 1995). Nevertheless, it has been estimated that there are still about 1,000,000 cases of tetanus per year globally (Thwaites 2003).

In developing countries, neonatal tetanus causes over 200,000 infant deaths per year, due largely to poor umbilical hygiene after childbirth. According to the World Health Organization (WHO), Somalia had the highest rate in 1999, with 16.5 neonatal tetanus deaths per 1000 live births (WHO 2000). Vaccination of mothers would prevent the majority of these cases and the WHO has campaigned to increase the coverage of vaccination in developing countries (Demicheli 2005; Vandelaer 2003; WHO 2007).

Although the molecular mechanisms of tetanus toxin in the initiation of pathogenesis are well known, the later stages of the pathological cascade are inadequately understood. There is evidence indicating that disturbances in autonomic control, with sympathetic overactivity (e.g. elevated blood pressure, rapid heart rate) could play a crucial role in the pathophysiology of severe tetanus cases (CDC 2007; Cook 2001). Recently, Thwaites 2006 reported data giving further support to the possible role of catecholamines (stress hormones) in tetanus. The concentrations of epinephrine and norepinephrine were much higher in tetanus patients than in other critically ill patients and, among the tetanus patients, the concentrations were higher in those who had more severe forms of tetanus.

There is evidence suggesting that vitamin C could affect tetanus. Vitamin C is involved in the synthesis of norepinephrine, and the adrenal glands have the highest concentration of the vitamin in the body (Diliberto 1991; Levine 1985; Patak 2004; Rice 2000). Furthermore, various infections and purified bacterial toxins lead to the depletion of vitamin C from the adrenal glands (Hemilä 2006). A few experimental studies found that vitamin C improved

the functions of phagocytes and the proliferation of T-lymphocytes indicating that it has a role in the immune system (*see references in Hemilä 2006*). In trials with humans, vitamin C reduced the duration and severity of the common cold and pneumonia (Douglas 2004; Hemilä 1999; Hemilä 2007). In dozens of animal studies, vitamin C has been shown to increase resistance against diverse infections and against a few purified bacterial toxins (Hemilä 2006). In particular, Dey 1966 reported that five rats administered twice the minimal lethal dose of tetanus toxin all died, whereas 25 rats administered vitamin C either before or after the toxin all lived (Hemilä 2006 p. 112). Vitamin C also reduced mortality in mice caused by toxins of several *Clostridium* species (Büller Souto 1939; Hemilä 2006 p. 115) In an early case report, Klenner 1954 described that vitamin C seemed to be beneficial in the treatment of tetanus in a 6-year-old boy.

Although vitamin C affects the immune system, it may be important only in particular conditions. For example, it is possible that variation in vitamin C intake does not affect the immune system in the ordinary western population because of their relatively high intake levels, but it may be a limiting factor in populations with low intakes. In the extreme, the prevalence of scurvy (i.e. frank vitamin C deficiency) was up to 44% in refugee camps in the Horn of Africa (WHO 1999).

Vitamin C is safe in high doses. Approximately 10 mg/day prevents scurvy but, according to USA nutritional recommendations, the 'tolerable upper intake level' is 2 g/day for adults (IOM 2000). The basis for this upper limit is the appearance of diarrhoea, which is, however, a trivial adverse effect that disappears quickly with a reduction in intake. There have been speculations of potential harms from high doses of vitamin C, but they have been shown to be unfounded (*see references in Hemilä 2006*). In a recent pharmacokinetic study, participants were administered up to 100 g of vitamin C intravenously over a few hours without adverse effects, indicating the safety of such very high single dose in healthy people (Padayatty 2004). Furthermore, Cathcart 1981 stated that patients with severe infections can take over 30 g/day of vitamin C orally without suffering from diarrhoea, possibly because of changes in vitamin C metabolism.

Tetanus is a severe infection afflicting hundreds of thousands of people annually and vitamin C is a safe and inexpensive essential nutrient. Therefore the possibility that vitamin C may have an action on tetanus is worthy of systematic consideration.

## OBJECTIVES

To determine the effectiveness of vitamin C supplementation for (1) preventing the development of tetanus in vaccinated and unvaccinated individuals and (2) reducing hospital stay and mortality in patients with a diagnosis of tetanus.

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

We will restrict the analysis to controlled clinical trials, and will include both randomized and non-randomized trials. The use of placebo is not required for two reasons. First, it is unlikely that being aware of taking or not taking vitamin C would itself affect the occurrence or prognosis of such a severe infection as tetanus. Second, a recent meta-analysis of trials comparing a placebo group with a no-treatment group found no evidence of a placebo effect on binary outcomes and only weak evidence that placebo may affect outcomes measuring pain (Hrobjartsson 2001; Hrobjartsson 2005).

### Types of participants

We will include studies involving people of any age and sex, either vaccinated or unvaccinated (prevention) or who have a diagnosed condition of tetanus (treatment). In this review we will include both neonatal tetanus and tetanus cases occurring after the neonatal period.

### Types of intervention

Treatment with vitamin C should be the only systematic difference between the treatment arms. We will include studies comparing outcomes after administration of vitamin C (ascorbic acid or its salts or other derivatives) (orally or intravenously) with administration of no or a lower dose of vitamin C. We will not require placebo administration to the control group. We will not apply restrictions on the dosage and frequency of administration of vitamin C, and will include treatment trials using a single dose. Vitamin C may be administered with other treatments, but the other treatments must be equal in the groups compared.

'Prevention trial' indicates regular vitamin C administration for people who do not have tetanus, and 'treatment trial' indicates that vitamin C administration was initiated after the diagnosis of tetanus.

### Types of outcome measures

Prevention trials: The primary outcome will be the incidence of tetanus during vitamin C supplementation. Secondary outcomes will be the duration of hospital stay, the severity of symptoms, and complications.

Treatment trials: The primary outcomes will be the duration of hospital stay and mortality caused by tetanus. Secondary outcomes will be measures of severity and the occurrence of complications such as fractures and nosocomial infections.

Our operational definition of tetanus will be the disease that the original authors classify as tetanus.

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Wounds Group methods used in reviews.

We will search the following databases:

The Wounds Group Specialised Register;

The Infectious Diseases Group Specialised Register;

The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* latest issue);

MEDLINE (1966 to present);

OLD MEDLINE (1950 to 1965);

EMBASE (1990 to present).

We will use the following combination of MeSH and free text terms:

1 exp Tetanus/

2 exp Tetanus Toxin/

3 exp Tetanus Toxoid/

4 tetanus.mp.

5 or/1-4

6 exp Ascorbic Acid/

7 ascorb\$.mp.

8 vitamin\$ adj5 C.mp.

9 or/6-8

10 5 and 9

When necessary, we will adapt these terms to allow for variations in indexing between databases. We will not apply language restrictions.

Previously, Briggs 1984 carried out extensive literature searches and published a bibliography containing 413 references to papers related to vitamin C and infections, which we will search. We will also search the reference lists of all other pertinent reviews and of the potentially eligible studies identified in our search.

## METHODS OF THE REVIEW

The first author will search the literature and both authors will assess independently the extracted titles and abstracts to identify potentially relevant articles. We will obtain full versions of all potentially eligible articles, which we will scrutinize independently. We will exclude trials failing to meet the inclusion criteria. In cases of disagreement on the relevance of particular articles, we will attempt to reach a consensus and describe the divergent opinions in the review if that seems appropriate. Unpublished trials, if identified, will be considered in a similar way as published trials.

Both authors will independently extract pertinent data from the articles selected and, in case of differences in the interpretation of study findings, we will seek a consensus. We will record the following quality features of the trials on data extraction forms: randomized allocation (yes, no, unclear), allocation concealment (yes, no, unclear), blinding of participants (yes, no, unclear),

blinding of investigator (yes, no, unclear), blinding of outcome assessor (yes, no, unclear), blind data analysis (yes, no, unclear), baseline measurements, dropout proportion during follow up, intention-to-treat analysis (yes, no, unclear), and to a free text field we will record other possibly relevant features that may affect trial validity. For a detailed discussion of these quality items, see Higgins 2006 chapter 6.

We will not calculate any quality scores for selected trials because “quality scores are at best useless and at worst misleading” (Greenland 1994). The Cochrane Reviewers’ Handbook states that “reviewers should avoid the use of ‘quality scores’ and undue reliance on detailed quality assessments. It is not supported by empirical evidence, it can be time-consuming, and it is potentially misleading” (Higgins 2006). Furthermore, even though shortcomings in the design and conduct of trials may lead to erroneous conclusions (Higgins 2006), a recent meta-analysis of 276 randomized controlled trials (RCTs) found that double blinding and allocation concealment, two quality measures that are frequently used in meta-analyses, were not associated with treatment effects (Balk 2002). We agree with the Shapiro 1997 comment that “quality is best evaluated qualitatively ... the author should give reasons for judging the quality of any given study as good or bad in transparent and easily comprehensible language. It is then up to the reader to decide whether he agrees or disagrees.” Following such reasoning, we will describe the weaknesses and strengths of trials explicitly in ‘Description of included’ section and we will consider how features of the trials set limits to conclusions in the ‘Discussion’ section.

We will enter the data and analyse it using Cochrane RevMan software, presenting the results with 95% confidence intervals (CI). We will use two-tailed P values in this review.

We will report estimates for the incidence of tetanus and for mortality (dichotomous outcomes) as relative risk (RR). If we identify several trials reporting days of hospitalization (continuous outcome), we will calculate the relative effect of vitamin C, normalizing the mean and standard deviation (SD) values by dividing them by the mean of the control group, thus determining the percentage effect of vitamin C on the outcome. The reason for this normalization is that the duration of hospitalization in the control group may vary substantially between different trials, and thus the measurement scales of the trials would be inconsistent if not normalized. If we identify several trials reporting the severity of tetanus (continuous outcome), we will calculate the standardized mean differences and overall effect size.

We will include both neonatal tetanus and tetanus cases occurring after the neonatal period, but we will analyse them separately because they are clinically different categories. We will also analyse separately trials with unvaccinated and vaccinated participants.

If a number of trials are available with sufficient uniformity in the setting and outcome, we will assess heterogeneity using the

I<sup>2</sup> statistic (Higgins 2003). This examines the percentage of total variation across studies due to heterogeneity rather than chance. Value of I<sup>2</sup> over about 70% indicates a high level of heterogeneity. If several trials are similar in the setting and outcome, we will attempt pooling, but if trials are dissimilar, we will present their results separately.

We are expecting few trials falling to the inclusion criteria and investigations of heterogeneity when there are very few studies are of questionable value. Explorations of heterogeneity that are devised after heterogeneity is identified should be interpreted cautiously (Higgins 2006 sect 8.7.3). Based on biological considerations, we pre-specify the following subgroup analyses:

For the inclusion of trials, we will not set limits to vitamin C doses, but we will carry out subgroup analyses based on the doses. In the case of: (1) preventive trials we will set the limit of subgroup analysis to 100 mg/day because this is close to the dosage leading to maximum vitamin C levels in the plasma of healthy people; and (2) treatment trials we will set the limit to 1000 mg/day because there is evidence of changes in vitamin C metabolism caused by bacterial toxins. Low doses may lead to negative findings because the dose may simply be too low, whereas studies with high doses are more definitive. If several trials report dietary vitamin C levels and these vary between trials, we will carry out subgroup analysis by separating trials to those with low and high dietary vitamin C

levels. If results are published by subgroups of severity of disease at baseline, we will present the data separately in the severity groups.

If we find, in the analysis phase, further characteristics that may explain heterogeneity between or within identified trials, we will be cautious in the interpretation of the findings.

## POTENTIAL CONFLICT OF INTEREST

None for either author

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