Vitamin C for preventing and treating tetanus (Review)

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 2

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TABLE OF CONTENTS

[Intervention Review]

Vitamin C for preventing and treating tetanus

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Editorial group: Cochrane Wounds Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 10, 2011.
Review content assessed as up-to-date: 25 August 2011.

Citation: Hemilä H, Koivula T. Vitamin C for preventing and treating tetanus. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD006665. DOI: 10.1002/14651858.CD006665.pub2.

ABSTRACT

Background

Tetanus is a severe disease that can be prevented by vaccination. In developing countries vaccination coverage is not always high, and cases still occur in developed countries, particularly in elderly people owing to their reduced immuno protection. There are hundreds of thousands of tetanus cases per year globally. In animal studies, vitamin C has protected against various infections. In a study with rats, vitamin C protected against the purified tetanus toxin.

Objectives

To assess the prophylactic and therapeutic effect of vitamin C on tetanus.

Search methods

We searched the Cochrane Wounds Group Specialised Register (searched 4 August 2011); Cochrane Infectious Diseases Group Specialised Register (Searched 24 August 2011); The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 3); Ovid MEDLINE (1950 to August Week 2 2011); Ovid MEDLINE (In-Process & Other Non-Indexed Citations August 18, 2011); and Ovid EMBASE (2009 to 2010 Week 50) and the reference lists of relevant reviews and monographs.

Selection criteria

Controlled trials of vitamin C as a prevention or treatment for tetanus, whether or not these were placebo controlled, in any language, published or unpublished. Two authors independently made inclusion decisions.

Data collection and analysis

Both review authors independently extracted data from trial reports and assessed methodological quality. We calculated the relative risk of death by using the RevMan computer program and odds ratio by using the StatXact computer program.

Main results

One single trial was eligible for inclusion. This non-randomised, controlled, unblinded trial undertaken in Bangladesh involved 117 tetanus patients. Vitamin C at a dosage of 1 g/day was administered intravenously alongside conventional treatment. At recruitment, the participants were stratified into two age groups and the results were reported by age. In the children aged 1 to 12 years (n = 62), vitamin C treatment was associated with a 100% reduction in tetanus mortality (95% CI from -100% to -94%). In people aged 13 to 30 years (n = 55), vitamin C treatment was associated with a 45% reduction in tetanus mortality (95% CI from -69% to -5%).

Authors' conclusions

A single, non-randomised, poorly reported trial of vitamin C as a treatment for tetanus suggests a considerable reduction in mortality. However, concerns about trial quality mean that this result must be interpreted with caution and that vitamin C cannot be recommended as a treatment for tetanus on the basis of this evidence. New trials should be carried out to examine the effect of vitamin C on tetanus treatment.

PLAIN LANGUAGE SUMMARY

Vitamin C for preventing and treating tetanus

Tetanus is a disease caused by tetanus toxin, which is produced by the bacterium *Clostridium tetani*. This bacterium typically infects penetrating wounds contaminated by foreign material such as soil. In developing countries, poor hygiene after childbirth may cause tetanus in newborn babies. Even though vaccination has dramatically decreased the burden of tetanus, there are still hundreds of thousands of cases per year globally. We found one controlled trial that examined whether one gram per day of intravenous vitamin C would help in the treatment of tetanus patients. Vitamin C was used alongside standard treatments for tetanus. Intravenous vitamin C reduced the mortality of children aged between 1 and 12 with tetanus by 100% and that of 13 to 30 year old patients by 45%. The trial was not properly conducted and caution is required in the interpretation of the findings. Vitamin C cannot be recommended as a treatment for tetanus on the basis of this single study. Further investigation of the role of vitamin C in tetanus treatment is warranted.

BACKGROUND

Description of the condition

'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 clinically. The clinical picture is dominated by muscle spasms and rigidity. Often the first sign is rigidity of the jaw muscles, followed by stiffness of the neck, difficulty in swallowing, and rigidity of the abdominal muscles. Other symptoms include elevated temperature, raised blood pressure, and an episodically rapid heart rate. Tetanus may lead to complications such as fractures of the spine or long bones because of contractions and convulsions, and to pulmonary embolism, bed sores and nosocomial infections due to prolonged hospitalisation. The current treatment of tetanus consists, for example, of surgical debridement of the wound and antibiotic therapy (metronidazole) to remove the source of infection, tetanus immune globulin to neutralize circulating toxin, and benzodiazepine for sedation and muscle relaxation (Bleck 2005; CDC 2009; Cook 2001; Farrar 2000; Rhee 2005; Thwaites 2006a; WHO 2009).

Tetanus is typically caused by anaerobic bacterial growth in a contaminated penetrating wound. Vaccination against tetanus has dramatically reduced the incidence of the disease in developed countries, but infrequent cases occur, particularly in elderly people owing to reduced immuno protection (Gergen 1995). Nevertheless, hundreds of thousands of tetanus cases per year occur globally (Thwaites 2003).

In developing countries, neonatal tetanus causes over 100,000 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; Roper 2007; WHO 2000; WHO 2009).

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 (Cook 2001; CDC 2009; Daher 1997; Wasay 2005). Recently, Thwaites 2006b reported data supporting 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, amongst the tetanus patients, the concentrations were higher in those who had more severe forms of tetanus.

Description of the intervention

Vitamin C was identified in the 1930s in the search for the substance deficiencies that cause scurvy. After the identification there was much interest in its effects on diseases unrelated to scurvy, but the role of vitamin C on other diseases is still unsettled. Vitamin C supplementation shortened the duration of colds (Hemilä 2007b) and prevented pneumonia in three trials with participants under special circumstances (Hemilä 2007a). Dietary vitamin C intake modified the effect of vitamin E on the mortality of male smokers (Hemilä 2009). Although such findings indicate that the effects of vitamin C are not limited to preventing scurvy, their practical significance is not clear.

In an early case report, Klenner 1954 described that vitamin C seemed to be beneficial for an unvaccinated six-year-old boy who contracted tetanus. However, vitamin C was used in addition to tetanus antitoxin, penicillin, adrenal cortex extract and Tolserol (mephenesin, muscle relaxant). Although the boy was cured and discharged from hospital on the 18th day, the specific role of vitamin C in the curing process cannot be inferred from the report.

Usually vitamin C is administered as tablets, but it can also be administered intravenously. A recent pharmacokinetic study compared oral and intravenous administration and found substantially higher plasma levels when vitamin C was administered by intravenous route compared with oral administration (Padayatty 2004). The highest dose used in the pharmacokinetic study, 100 g of vitamin C intravenously given over a few hours, increased the plasma concentration peak to 15,000 μmol/L, which is over 100 times the plateau level reached by oral administration (Levine 1996; Padayatty 2004).

Vitamin C is safe in high doses. A dose of approximately 10 mg/day prevents scurvy but, according to the US 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. Several other reviewers have also concluded that vitamin C is safe in doses ranging to several grams per day (Hathcock 2005; Hemilä 2006; Rivers 1987).

How the intervention might work

As described above, sympathetic overactivity with elevated levels of catecholamines may pay a role in the pathophysiology of tetanus. Vitamin C is involved in the synthesis of norepinephrine, and the adrenal glands have the highest concentration of this vitamin in the body (Diliberto 1991; Levine 1985; Patak 2004; Rice 2000). Various infections and purified bacterial toxins lead to the depletion of vitamin C from the adrenal glands (Hemilä 2006). A few experimental studies have shown that vitamin C improved the functions of phagocytes and the proliferation of T-lymphocytes, indicating that it has a role in the immune system (Hemilä 2006). In dozens of animal studies, vitamin C increased resistance against diverse infections and 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). Vitamin C also reduced mortality in mice caused by toxins of several *Clostridium* species (Büller Souto 1939; Hemilä 2006).

Chakrabarti 1955 reported that tetanus patients had lower plasma vitamin C levels than healthy people, and tetanus patients who died had lower levels than those who survived. Furthermore, tetanus patients had elevated levels of dehydroascorbate, which is the oxidized form of vitamin C. Such changes in vitamin C metabolism provide a further rationale to test vitamin C for tetanus patients.

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

Why it is important to do this review

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

Links to the publications cited in this Background section, for which full text versions are available, can be found at: www.ltdk.helsinki.fi/users/hemila/CT.

OBJECTIVES

To determine the effects of vitamin C supplementation for:

(1) preventing the development of tetanus in vaccinated and unvaccinated individuals;

(2) treating patients with a diagnosis of tetanus.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled clinical trials, both randomised and non-randomised. The review includes studies with and without placebo control since, firstly, it is unlikely that being aware of taking or not taking vitamin C would influence such a severe disease as tetanus; and secondly, 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, although placebo did have an effect on pain measured as a continuous outcome (Hrobjartsson 2001; Hrobjartsson 2010).

Types of participants

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

Types of interventions

Studies in which treatment with vitamin C was the only systematic difference between the treatment arms were eligible for inclusion. We included studies comparing outcomes after the administration of vitamin C (ascorbic acid or its salts or other derivatives; orally or intravenously) with the administration of no or a lower dose of vitamin C. We did not apply restrictions on the dosage and frequency of administration of vitamin C, and we considered treatment trials using a single dose and trials in which vitamin C was administered with other treatments, provided co-interventions did not differ between the treatment arms. We regarded 'prevention trials' as those in which regular vitamin C was administered to people who did not have tetanus and 'treatment trials' as those in which vitamin C was administered after the diagnosis of tetanus.

Types of outcome measures

We applied any definition of tetanus applied by the original study authors.

Primary outcomes

Prevention trials:

1. Incidence of tetanus.

Treatment trials:

1. Mortality;
2. Duration of hospital stay.

Secondary outcomes

Prevention trials:

1. Mortality;
2. Duration of hospital stay;
3. Severity of symptoms and complications.

Treatment trials:

1. Severity and occurrence of complications such as fractures and nosocomial infections.

Search methods for identification of studies

Electronic searches

For an outline of the search methods used in first update of this review see Appendix 1.
For this second update the following databases and dates are covered:

- Cochrane Wounds Group Specialised Register (searched 4 August 2011);
- Cochrane Infectious Diseases Group Specialised Register (searched 24 August 2011);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 3);
- Ovid MEDLINE (1950 to August Week 2 2011);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations August 18, 2011);
- Ovid EMBASE (2009 to 2010 Week 50)

The following strategy was used to search The Cochrane Central Register of Controlled Trials (CENTRAL):
#1 MeSH descriptor Tetanus explode all trees
#2 tetanus
#3 (#1 OR #2)
#4 MeSH descriptor Ascorbic Acid explode all trees
#5 ascorb* or "vitamin C"
#6 (#4 OR #5)
#7 (#3 AND #6)
The search strategies for Ovid MEDLINE and Ovid EMBASE can be found in Appendix 2 and Appendix 3 respectively. No methodological filters were used. No date or language restrictions were applied.

Searching other resources

Previously, Briggs 1984 carried out extensive literature searches and published a bibliography containing over 400 references to papers related to vitamin C and infections, which we checked. We

also searched the reference lists of all other pertinent reviews and of the potentially eligible studies identified in our search.

Data collection and analysis

Selection of studies

The first review author searched the literature and both review authors independently assessed the titles and abstracts to identify potentially relevant articles. We obtained full versions of all potentially eligible articles, which we scrutinised independently.

Data extraction and management

Both review authors independently extracted pertinent data from the articles selected. We recorded the following quality features of the trials on data extraction forms as 'yes', 'no', 'unclear': randomised allocation, allocation concealment, blinding of participants, blinding of investigator, blinding of outcome assessor, blind data analysis and intention-to-treat analysis. We also recorded baseline measurements and percentage dropout during follow up. For a discussion of these quality items, see Higgins 2011 (chapter eight).

Assessment of risk of bias in included studies

We did not calculate any quality scores for selected trials because "quality scores are at best useless and at worst misleading" (Greenland 1994), and "the use of scales for assessing quality or risk of bias is explicitly discouraged in Cochrane reviews. " (Higgins 2011 sect 8.3.3). Furthermore, even though shortcomings in the design and conduct of trials may lead to erroneous conclusions (Higgins 2011 chapter 8), a recent meta-analysis of 276 randomised controlled trials 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 comprehensive language. It is then up to the reader to decide whether he agrees or disagrees." Following such reasoning, we decided to describe the weaknesses and strengths of trials explicitly in the 'Risk of bias in included studies' section.

Measures of treatment effect

We entered the case fatality rate data of the identified Jahan 1984 study to the RevMan 2009 computer program and calculated the relative risk (RR), presenting the results with 95% confidence intervals (CI). Because a cell of the 2×2 table was empty in one comparison and the RevMan algorithm is inappropriate for analysing such a table, we used the StatXact 2009 software (release 7) to calculate the exact 95% CI for the odds ratio (OR) as an approximation of RR (Rothman 1998). We also calculated the Fisher exact test P-value for the comparisons. We used two-tailed P values in this review.

Unit of analysis issues

The patients in the Jahan 1984 trial were divided into two wards by vitamin C administration. Although this may cause bias in treatment, it does not affect the unit of analysis (the individual patient), because tetanus is not a contagious disease.

Assessment of heterogeneity

We assessed heterogeneity using the I^2 statistic (Higgins 2003). This examines the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of I^2 greater than about 70% indicates a high level of heterogeneity.

Data synthesis

We did not pool the age groups of the Jahan 1984 trial, because there was a high level of heterogeneity.

RESULTS

Description of studies

See: Characteristics of included studies.

No new eligible trials were identified in the searches carried out for the first and second updates of this review. From the original search we found one eligible controlled trial that provided data pertinent to vitamin C in the treatment of tetanus patients (Jahan 1984), but we found no trials reporting on the prevention of tetanus with vitamin C. The main features of the Jahan trial are briefly summarised in the table 'Characteristics of included studies', but described in detail in the following section because the weaknesses and strengths are crucial when considering the validity of it's findings. The Jahan 1984 trial was carried out in Bangladesh in the early 1980s. A total of 117 tetanus patients were admitted to the Infectious Disease Hospital in Dhaka and divided into two age groups at recruitment. There were 62 children in the age group 1 to 12 years, and 55 children and adults in the age group 13 to 30 years. The Jahan report is available at www.ltdk.helsinki.fi/users/hemila/CT.

Risk of bias in included studies

Jahan 1984 did not describe the allocation method, but the vitamin C and control arms were of the same size: 31 compared with 31 in the younger age band; and 27 (vitamin C) compared with 28 (control) in the older participants. Allocation concealment could not be judged from the report. Patients allocated vitamin C received 1 g/day intravenously "in addition to conventional antitetanus therapy which included antitetanus serum, sedatives, antibiotics and muscle relaxant etc." (p 25). Participants allocated to the control arm received conventional antitetanus therapy but the administration of placebo is not mentioned. No baseline data, except for the age ranges, are presented for the two trial arms. There is no description of how tetanus was diagnosed. The authors present results for 117 patients in a table indicating that all recruited patients were included in the analysis. The trialists did not state the duration of intervention or their duration of follow-up, but stated that "patients succumbed to tetanus even three to four weeks after admission" (p 27).

Thus, the Jahan 1984 trial had two age groups with treatment and control arms of similar size and administration of vitamin C was the only systematic difference between them. However, the methodological description in the Jahan report is minimal. The role of the methodological shortcomings in the interpretation of the study results are considered in the 'Discussion' section.

We were able to contact the first author of the Jahan 1984 trial. To our query about the methods of the 1984 trial, we received this reply: "we selected two wards side by side. Patients of one ward were under treatment with vitamin C in addition to conventional treatments. In another ward patients were enrolled as a control group and got only the conventional treatment (without vitamin C). Age groups and the number of patients we tried to match as far as possible. Because we had to take the patients who were inpatients in the hospital we did not use a placebo. We were not able to hide the allocations from the physicians at that stage. Follow up of the patients was until they were discharged as fit persons or died. Diagnosis of the disease was done by a physician specialised in infectious diseases" (Professor Khursheed Jahan, 9 July 2007; personal letter).

Effects of interventions

Preventing tetanus

We did not identify any trials describing the effects of vitamin C as a prevention for tetanus.

Treating tetanus

Effect on case fatality rate

We identified one controlled trial that examined the effects of 1 g/day vitamin C given intravenously for patients with tetanus (Jahan 1984). At recruitment, the participants were stratified into two age groups and the results were reported by the age group.

Ages 1 to 12 years: vitamin C significantly reduced the case fatality rate (0/31; 0% mortality) compared with control (23/31; 74% mortality). According to RevMan, the relative risk (RR) of death (vitamin C relative to control) was 0.02 (95% CI from 0.00 to 0.34). Analysis 1.1; subgroup 1.

Ages 13 to 30 years: vitamin C significantly reduced the case fatality rate (10/27; 37% mortality) compared with control (19/28; 68% mortality). The RR of death was 0.55 (95% CI from 0.31 to 0.95). Analysis 1.1; subgroup 2.

The above RR and CI values were calculated using the RevMan program. However, there were no deaths in the younger tetanus patients administered vitamin C and in such a case RevMan adds 0.5 to each cell of the 2×2 table (Higgins 2011 sect 9.4.4), which leads to an erroneous estimate and P-value. Therefore, we used the StatXact program to calculate the exact CI of the odds ratio (OR) for the young patients: OR of death was 0.00 (95% CI from 0.00 to 0.06). The Fisher's exact test, which is valid for tables with an empty cell, gives $P=3\times10^{-10}$ for the comparison of vitamin C and control arms of the young patients, whereas the RevMan gives P=0.006. For the older tetanus patients, the RevMan algorithm and the Fisher exact test give the same P-value as expected because there were a reasonable number of deaths in both study arms.

Heterogeneity between the subgroups

We found strong evidence of heterogeneity in the effect of vitamin C between the young and old patients. The RevMan gives the I^2 value 90% indicating a high level of heterogeneity. Vitamin C had a greater effect in the younger participants. The authors of the Jahan 1984 trial reported the results of the age groups separately and they did not combine the results. We did not pool the age strata because of the high level of heterogeneity.

Sensitivity analysis based on the rejection of trials with lower methodological quality was not possible because we identified only one trial.

DISCUSSION

Quality of the evidence

We identified one trial that examined the therapeutic effect of vitamin C on the mortality of people with tetanus(Jahan 1984). In the first update of this review,no new trials were identified. The Jahan 1984 trial reported a highly significant benefit associated

with intravenous vitamin C on the case fatality rate of tetanus patients. The methods used in the Jahan trial were, however, unsatisfactory and superficially described. Here we will consider whether potential biases could explain the differences reported in the case fatality rate between the vitamin C and control arms.

Jahan 1984did not state an explicit case definition for tetanus. Although this is a shortcoming in the report, it does not seem reasonable to assume that tetanus was improperly diagnosed in an infectious diseases hospital in a country that had a high incidence of this disease (currently the incidence is lower). Furthermore, the trial author described in a personal letter that the diagnosis was by a "physician specialised in infectious diseases".

Selection bias operates when there are systematic differences between comparison groups at baseline. Adequate randomisation with allocation concealment guards against it. No data were presented by Jahan 1984 to allow us to judge whether the allocation process resulted in balanced allocation between treatment groups for prognostic factors. This trial was not randomised and there is a risk of selection bias (the ward a patient was allocated to determined whether they received vitamin C). However, it is highly unlikely that potential baseline differences could lead to such great difference in mortality between the study arms as reported for the younger patients**.**

Performance bias operates when there are systematic differences in the care provided apart from the intervention being evaluated. Jahan 1984 stated that both vitamin C and control arms received "conventional antitetanus therapy which included antitetanus serum, sedatives, antibiotics and muscle relaxant etc.", so the administration of vitamin C was the only systematic difference between the trial arms. However, the vitamin C and control patients were treated in different wards, which is unsatisfactory because aspects of treatment could be somewhat different between the two wards. Placebo was not used in Jahan 1984, but a recent meta-analysis found that, in trials examining various topics, placebo arms did not differ from no-treatment arms if the outcome was binary; e.g. mortality (Hrobjartsson 2010). Thus, the care providers may have been aware of which arm the patients had been enrolled into, but it is highly unlikely that such knowledge would have altered treatment to such an extent that it could explain the difference in mortality between the study arms as reported for the younger patients in Jahan 1984.

Attrition bias operates when there are large numbers of people who withdraw from the study or when the rates of withdrawal are different between treatment arms. Attrition bias is unlikely in Jahan 1984, since all patients allocated were followed up and analysed. Furthermore, in a personal letter, the trial author confirmed that all patients were followed up "until they were discharged as fit persons or died".

Detection bias operates when there are systematic differences in the ways outcomes were assessed between treatment groups and is more likely to occur when there is no blinded outcome assessment and when the outcome is subjective. It is unlikely, however, that detection bias is operating in Jahan 1984since the outcome was mortality which is not a subjective outcome. There is minimal possibility of bias in detecting mortality in a hospital.

Consequently, although the methods of the Jahan 1984 trial are poorly described and the trial was poorly conducted, the biases discussed above cannot explain the reported findings. There seems to be no basis to assume attrition bias or detection bias in the trial. Possibly there has been selection bias and performance bias to some degree, but this cannot explain the reported difference in outcomes among the younger participants. Glasziou 2007 argued that rate ratios beyond 10 are highly likely to reflect real treatment effects, even if confounding factors may contribute to the size of the observed effect. In the younger patients of the Jahan trial, the entire confidence interval and not just the point estimate is beyond the ratio of 10. In the older patients of the Jahan trial, the confidence interval of the vitamin C effect is close to the control group level, and therefore the results are not robust to the possibility of selection and performance biases. Nevertheless, the findings in the older patients are consistent with the findings in the younger patients.

Finally, the existence of a single positive study might be explained by publication bias, meaning that researchers tend to report studies with 'positive' results but not those with 'negative' results. With this reasoning, it is possible that Jahan 1984 was published just because vitamin C appeared beneficial (but simply by chance), whereas several trials might remain unpublished because of their negative results. Publication bias may explain findings that are close to statistical significance, but it is an unlikely explanation for highly statistically significant findings such as those of the younger patients in the Jahan 1984 trial. Furthermore, it would seem incomprehensible that publication bias would generate the highly significant difference between the age groups. Therefore we do not consider that publication bias is relevant in this case.

Applicability of the evidence

The Jahan 1984 trial is methodologically unsatisfactory and great caution is required in the interpretation of the results; also because there are no other trials giving independent support to the findings. Nevertheless, a few animal studies are consistent with the concept that vitamin C might protect against clostridial toxins (Büller Souto 1939; Dey 1966).

In Jahan 1984, vitamin C was used over and above treatments that are still used for treating tetanus patients. In this respect, the trial is not outdated.

When considering extrapolation of the findings of vitamin C trials, an issue of particular importance is the level of dietary vitamin C intake. A different outcome between the vitamin C and control arms may result from a particularly low dietary intake in the control arm ('marginal vitamin C deficiency') or from the high dose supplementation in the vitamin C arm. In the former case, a small dosage of supplement may produce a similar effect, whereas

in the latter case the high dose is necessary. As reference levels: scurvy may be caused by vitamin C intake of less than 10 mg/day, whereas the mean vitamin C intake, for example, in the USA is about 100 mg/day (IOM 2000).

If the biological basis for the results in Jahan 1984 was the treatment of marginal deficiency, this would not provide an explanation for the significant heterogeneity between the age groups, as the dose is so high that it would cure marginal deficiency in both age groups. Thus, it is possible that the high dose, 1 g/day, was essential for the results. Furthermore, the benefit of vitamin C was significantly greater for the younger patients (1 to 12 years), who weigh on average less than the older patients (13 to 30 years). Thus the heterogeneity might have resulted from dose dependency because the dose per weight is higher in the younger patients. However, there are numerous other differences between the younger and older patients, and some of them might explain the heterogeneity as well. Therefore, dose dependency should be considered as only one of the possible reasons for the high level of heterogeneity between the age groups.

In the Jahan 1984 trial, vitamin C was administered intravenously which increases plasma level substantially more than oral administration (Padayatty 2004). Therefore, the same dose of vitamin C as tablets might not have similar effects.

Safety of vitamin C

In the Jahan 1984 trial, no adverse effects related to the intravenous 1 g/day vitamin C administration were mentioned.

There is evidence indicating that high dose vitamin C is usually safe when administered intravenously. A matched case control study of cancer patients found that 10 g/day vitamin C by intravenous infusion for 10 days and orally thereafter was associated with a longer survival time which indicates the absence of harmful effects with such a dosage (Cameron 1976). High intravenous vitamin C doses, up to 65 g twice per week for 10 months, have also been reported for cancer patients (Padayatty 2006). A case report described the use of intravenous vitamin C doses at levels up to 28 g/day for a six-year-old boy with tetanus (Klenner 1954). There are few reports of severe harm caused by high-dose vitamin C administration. Furthermore, the death of a 68-year-old African American man was not attributed to the intravenous injection of 80 grams of vitamin C on two consecutive days per se, but to his coincident glucose-6-phosphate dehydrogenase deficiency (Campbell 1975). Consequently, there seems to be no concern about the safety of the intravenous dosage level, 1 g/day, used in Jahan 1984.

Cathcart 1981 stated that patients with severe infections can take over 30 g/day of vitamin C orally without suffering from diarrhoea, whereas healthy people can take only 4 to 10 g/day. This difference in tolerable doses may be caused by the changes in vitamin C metabolism because of severe infections (Chakrabarti 1955; Hemilä 2006). Thus, it is possible that the range of safe doses extends to higher levels in people who have severe infections compared with healthy people. Nevertheless, in a pharmacokinetic study, no adverse effects were reported with the administration of up to 100 g of vitamin C intravenously to healthy people (Padayatty 2004).

AUTHORS' CONCLUSIONS

Implications for practice

A single poor quality and poorly reported controlled trial found that 1 g/day intravenous vitamin C significantly reduced death rates in people with tetanus. The poor quality of this trial means that routine vitamin C use cannot be recommended on the basis of this trial alone. There were no evaluations of vitamin C as a prevention for tetanus.

Implications for research

Treatment trials: more research is needed into the effect of vitamin C on mortality of tetanus patients. Vitamin C should be studied as an addition to conventional therapy.

Prevention trials: because of vaccination, tetanus is nearly non-existent in children and middle-aged people in the developed world. Although vaccination should be a priority in developing countries, the prophylactic effects of vitamin C supplementation might be investigated in populations with a high incidence of tetanus.

ACKNOWLEDGEMENTS

We are grateful to Sally Bell-Syer, Duncan Chambers, Nicky Cullum, Ruth Foxlee, Andrew Jull, Andrea Nelson, Louise Thwaites, Gill Worthy and Amy Zelmer for their comments on improving the draft review, and for Margaret Carver for copy editing the review. Thanks to Helena Mullineaux who copy edited the updated review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Jahan 1984

Methods	Non randomised; allocation method not described. Vitamin C and control participants treated in separate wards. No placebo; no blinding. Duration up to 4 weeks.
Participants	117 tetanus patients admitted to the Infectious Disease Hospital, Dhaka, Bangladesh. Age group 1 to 12 years: 31 vitamin C, 31 control. Age group 13 to 30 years: 27 vitamin C, 28 control.
Interventions	Vitamin C intravenously 1 g/day vs. no vitamin C. Both groups received standard treatment
Outcomes	Case fatality rate.
Notes	Poorly described trial (see Risk of bias in included studies). Additional information was received from the first author, Professor Jahan

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Inadequate

DATA AND ANALYSES

Comparison 1. Vitamin C vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Case fatality rate	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 aged 1 to 12 years	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.02 [0.00, 0.34]
1.2 aged 13 to 30 years	1	55	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.31, 0.95]

Analysis 1.1. Comparison 1 Vitamin C vs control, Outcome 1 Case fatality rate.

Review: Vitamin C for preventing and treating tetanus

Comparison: 1 Vitamin C vs control

Outcome: 1 Case fatality rate

Study or subgroup	Vitamin C n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 aged 1 to 12 years					
Jahan 1984	0/31	23/31		100.0 %	0.02 [0.00, 0.34]
Subtotal (95% CI)	**31**	**31**		**100.0 %**	**0.02 [0.00, 0.34]**
Total events: 0 (Vitamin C), 23 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.74 (P = 0.0062)					
2 aged 13 to 30 years					
Jahan 1984	10/27	19/28		100.0 %	0.55 [0.31, 0.95]
Subtotal (95% CI)	**27**	**28**		**100.0 %**	**0.55 [0.31, 0.95]**
Total events: 10 (Vitamin C), 19 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.14 (P = 0.032)					

APPENDICES

Appendix 1. Search methods for the first review update (2009)

Electronic searches

For this first update we searched the following electronic databases:
Cochrane Wounds Group Specialised Register (Searched 11/11/09);
Cochrane Infectious Diseases Group Specialised Register (Searched 23/11/09);
The Cochrane Central Register of Controlled Trials (CENTRAL) - The Cochrane Library 2008 Issue 4;
Ovid MEDLINE - 1950 to 2009 Nov Week 1;
Ovid EMBASE - 2005 to 2009 Week 45.
The following strategy was used to search The Cochrane Central Register of Controlled Trials (CENTRAL):
#1 MeSH descriptor Tetanus explode all trees
#2 tetanus
#3 (#1 OR #2)
#4 MeSH descriptor Ascorbic Acid explode all trees
#5 ascorb* or "vitamin C"
#6 (#4 OR #5)
#7 (#3 AND #6)
The search strategies for Ovid MEDLINE and Ovid EMBASE can be found in Appendix 2 and Appendix 3 respectively. No methodological filters were used. No date or language restrictions were applied.

Searching other resources

We searched the review by Briggs 1984 and the books by Levy 2002 and Stone 1972, which list extensively the older literature related to vitamin C and infections. We also searched the reference lists of all other pertinent reviews and of the potentially eligible studies identified in our search.

Appendix 2. Ovid MEDLINE search strategy

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

Appendix 3. Ovid EMBASE search strategy

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

WHAT'S NEW

Last assessed as up-to-date: 25 August 2011.

Date	Event	Description
26 August 2011	New search has been performed	Second update, new search, no new trials identified, conclusions not changed

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 2, 2008

Date	Event	Description
19 November 2009	New search has been performed	New search, no new trials identified, conclusions not changed
11 November 2008	Amended	Contact details updated
6 August 2008	Amended	Converted to new review format
15 January 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

HH wrote the draft of the protocol and TK commented on the draft. HH carried out the literature searches. Both authors assessed the search results to identify potentially relevant articles and extracted data from the articles selected. HH carried out the statistical analysis and wrote the draft of the review and TK commented on the draft. HH updated the review.

DECLARATIONS OF INTEREST

No conflicts of interest for Harri Hemilä and Teija Koivula.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR/Department of Health (England), (Cochrane Wounds Group), UK.

NOTES

Links to full text papers cited in this review are available at: www.ltdk.helsinki.fi/users/hemila/CT.

INDEX TERMS

Medical Subject Headings (MeSH)

Ascorbic Acid [*therapeutic use]; Bangladesh; Tetanus [*drug therapy; mortality]; Vitamins [*therapeutic use]

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Humans; Infant