Mega-dose vitamin C in treatment of the common cold: a randomised controlled trial

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A RECENT COCHRANE systematic review of the effects of vitamin C on the common cold concluded that large maintenance doses of vitamin C do not lower the incidence of colds in well-nourished subjects in Western countries.[1] Nevertheless, the meta-analysis of 17 trials found that prophylactic doses of at least 1g per day were associated with a statistically significant weighted mean reduction in symptom days of about 0.45 days per cold (9% of symptom days).[1]

However, the authors of the Cochrane review could not draw conclusions about the therapeutic effects of vitamin C (ie, effects when taken at onset of a cold).[1] Findings of four well-conducted trials of the effects of treating colds with a loading dose of vitamin C were inconclusive[2-5] (Box 1). This prompted us to design a study to answer the question "Would vitamin C, when used exclusively as a therapeutic agent in doses that greatly exceed the required daily intake, reduce the duration or severity of symptoms of the common cold in healthy Australian adults?".

Objective: To determine the effect of large doses of vitamin C in the treatment of the common cold.

Study design: Double-blind, randomised clinical trial with four intervention arms: vitamin C at daily doses of 0.03 g ("placebo"), 1 g, 3g, or 3g with additives ("Bio-C") taken at onset of a cold and for the following two days.

Participants and setting: 400 healthy volunteers were recruited from staff and students of the Australian National University, Canberra, ACT, between May 1998 and November 1999. The trial continued for 18 months.

Interventions: Participants were instructed to commence medication when they had experienced early symptoms of a cold for four hours, and to record daily their symptoms, severity, doctor visits and use of other medications.

Main outcome measures: Duration of symptoms and cold episodes; cumulative symptom severity scores after 7, 14 and 28 days; doctor visits; and whether participants guessed which medication they were taking.

Results: 149 participants returned records for 184 cold episodes. No significant differences were observed in any measure of cold duration or severity between the four medication groups. Although differences were not significant, the placebo group had the shortest duration of nasal, systemic and overall symptoms, and the lowest mean severity score at 14 days, and the second lowest at 7 and 28 days.

Conclusions: Doses of vitamin C in excess of 1g daily taken shortly after onset of a cold did not reduce the duration or severity of cold symptoms in healthy adult volunteers when compared with a vitamin C dose less than the minimum recommended daily intake.

MJA 2001; 175: 359-362

METHODS

Our study was a double-blind, randomised trial comparing the effects of different doses and formulations of vitamin C. We chose as "placebo" a dose of 0.03g per day of vitamin C (about half the recommended minimum daily intake), recognising that all participants would have some nutritional vitamin C intake. Ethics approval was obtained from the Human Ethics Committee of the Australian National University, Canberra.

Participants

Staff and students of the Australian National University, Canberra, ACT, were recruited between May 1998 and November 1999 through personal letters and emails, announcements at student gatherings and direct approach in university common areas. Volunteers were eligible for the study if they were aged over 18 years, not pregnant or planning to become pregnant, in good general health, and did not take vitamin supplements regularly or take vitamin C, echinacea, zinc or Chinese herbal preparations regularly at the onset of a cold. Volunteers were clearly informed about the objectives of the study and signed an informed consent form. They also completed a questionnaire about their current health and medication status, including respiratory infections in the previous year. An information letter was provided for their general practitioners. Participants who returned information on one respiratory event were eligible to re-enrol in the study.

Interventions

Participants were randomised to receive one of four interventions: vitamin C in a daily dose of 0.03 g, 1 g or 3 g, or "Bio-

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1: Previous randomised controlled trials of the therapeutic effect of high-dose vitamin C on cold symptoms

Study	Participants and setting	Interventions	Outcomes
Anderson et al[2] (1974)	Toronto, Canada Hospital and business employees (> 275 per arm)	4 arms: 2 placebo, 2 therapeutic (4 g or 8 g vitamin C taken on day of symptom onset)	The two placebo arms unfortunately differed in outcome. Mean days of respiratory symptoms over 3 months: placebo, 5.4 and 4.16 days (combined placebo mean, 4.77 days); intervention, 4.82 days (4 g dose) and 4.52 days (8 g)
Karlowski et al[3] (1975)	Bethesda, USA National Institutes of Health employees (46 placebo, 43 therapy)	3 g vitamin C daily or placebo for the first 5 days of a cold	Problem in blinding, as over half the participants correctly guessed their medication through taste. Although mean duration of colds was longer in the placebo than therapy group (7.1 v 6.5 days), difference was confined to those who guessed their medication ("unblinded"). Unblinded group: 8.6 (placebo) v 4.7 days (therapy); blinded group: 6.3 (placebo) versus 6.7 days (therapy).
Elwood et al[4] (1977)	South Wales, UK Community volunteers (119 placebo, 145 therapy)	3 g vitamin C daily or placebo for 3 days	Vitamin C significantly reduced duration of "simple" colds in men (5.7 days [placebo] v 3.97 days [therapy]), but had no benefit in women (4.97 days [placebo] v 6.05 [therapy]), or in "chest" colds in either sex.
Tyrrell et al[5] (1977)	Salisbury, UK 482 volunteers	4 g of vitamin C or an identical-tasting placebo daily for 2.5 days	No evidence that vitamin C alleviated or shortened upper respiratory or general constitutional symptoms.

C" (containing vitamin C [3g daily] plus bioflavenoids [75 mg], rutin [150mg], hisperidin [150mg], rose hip extract [750mg] and acerola [150mg]). They were to take the medication at onset of cold symptoms and on the following two days.

The medications were prepared by Blackmores Ltd (Sydney, NSW) as compressed tablets with identical appearance and packaging. Dosage was confirmed by chemical analysis of unused tablets at the end of the study.

A random number table was constructed to order the medications sequentially so that each sequence of four numbers comprised all four types of medication. The medications were issued to investigators in 400 sequentially numbered sets of three bottles, each bottle containing the daily dose in three tablets. As volunteers joined the study they were given a set of three bottles and a correspondingly numbered "respiratory event card" to record outcome. The code was retained by the manufacturer until we were ready to analyse the results.

Participants were instructed that they must have at least two of the following symptoms for a minimum of four hours before commencing medication: sore or scratchy throat, nasal congestion or discharge, headache or stinging eyes, muscle aches, fever, or "four hours of certainty that a cold is coming on". On the first day of illness, they were to take the contents of one bottle (three tablets) as soon as possible. For the next two days, they were to take three tablets a day at intervals of at least four hours.

Outcome measures

The respiratory event card was designed to be carried in a wallet or purse. When a cold began, participants were instructed to score symptoms daily, noting presence and severity (1, mild; 2, moderate; or 3, severe) of cough, nasal, throat, and systemic symptoms, including fever, headache, aches, feeling unwell and "other symptoms". Recording was to cease either when all symptoms disappeared or 28 days after onset of the cold.

Participants were also instructed to record hours between onset of symptoms and first dose of medication, use of other medication and whether they sought medical attention. They were also invited to guess to which medication group they had been assigned.

Duration of the cold was measured from day of symptom onset to the last day of any symptom. Cold severity scores were the sum of daily individual symptom scores throughout the duration of the cold. Symptom days and severity scores for cough, nasal, throat and systemic symptoms were considered separately, and cumulative scores were considered at 7, 14, and 28 days. For any one day of symptoms, the maximum severity score was 12. Participants who did not return a respiratory event card were sent reminder letters after nine months and 15 months. The initial 12-month study period was extended by six months in an effort to increase the response rate.

Statistical analysis

We aimed to study 75 individuals in each intervention arm, in the expectation that the study would have an 80% power to detect a 30% difference between groups in duration or severity, which we considered clinically significant. Desired sample size was calculated assuming a mean duration of seven days and a standard deviation of four days.

Statistical comparisons were carried out using the software package SPSS.[6] Distribution, mean and median of duration and severity scores for each symptom were compared between the four groups by r-tests, analysis of variance and box plots.

RESULTS

Study population

Four hundred sets of medication were distributed to 323 volunteers. By November 1999, when the study was terminated, 149 people had returned completed respiratory event cards for 184 cold episodes. These 149 were sig-

2: Characteristics of participants and outcomes of a study of the effect of therapeutic vitamin C on the common cold

	Vitamin C formulation (daily dose)				
	0.03 g (*n* = 42)*	1 g (*n* = 47)*	3 g (*n* = 50)*	"Bio C" (3 g plus additives) (*n* = 45)*	Total (*n* = 184)*
Participant characteristics					
Mean age in years (95% CI)	38.6 (34.2–43.0)	40.1 (35.8–44.4)	39.9 (36.2–43.6)	45.1 (40.6–49.5)†	40.9 (38.8–43.0)
Male sex (95% CI)	45% (30%–61%)	38% (26%–54%)	50% (36%–65%)	51% (36%–66%)	46% (39%–54%)
Cold history in previous year					
Mean number of colds (95% CI)	2.2 (1.7–2.7) (*n* = 40)	2.25 (1.9–2.6) (*n* = 46)	2.2 (1.8–2.7) (*n* = 49)	1.5 (1.3-1.8)† (*n* = 44)	2.1 (1.9–2.3) (*n* = 179)
Mean number of days unwell from colds (95% CI)	8.0 (3.4–12.5) (*n* = 39)	7.7 (6.2–9.3) (*n* = 46)	7.7 (6.5–9.2) (*n* = 49)	6.8 (5.4–8.2) (*n* = 43)	7.5 (6.4–8.9) (*n* = 177)
Mean hours from symptom onset to medication (95% CI)	13.3 (9.4–17.2) (*n* = 39)	11.6 (8.7–14.7) (*n* = 44)	10.2 (8.2–12.3) (*n* = 48)	18.6 (11.2–26) (*n* = 44)	13.4 (11.1–15.8) (*n* = 175)
Outcome measures					
Mean days of symptom (95% CI)	8.5 (6.6–10.5)	10.1 (8.1–12.1)	10.4 (8.5–12.2)	9.9 (7.9–11.9)	9.8 (8.8–10.7)
Cough	5.3 (3.0–7.6)	6.4 (4.1–8.6)	6.3 (4.4–8.3)	4.4 (2.2–6.5)	5.6 (4.6–6.7)
Nasal symptoms	7.3 (5.4–9.1)	8.4 (6.7–10.1)	9.2 (7.4–11.1)	8.1 (6.1–10.1)	8.3 (7.4–9.2)
Throat symptoms	5.4 (3.6–7.2)	6.1 (4.3–7.9)	6.3 (4.6–7.9)	5.4 (3.8–6.9)	5.8 (5.0–6.7)
Systemic symptoms	3.5 (2.1–4.9)	3.7 (2.3–5.2)	3.8 (2.7–4.8)	4.4 (3.2–5.6)	3.9 (3.2–4.5)
Mean severity score‡ (95% CI)					
Day 7	20.2 (16.5–24.0)	22.1 (18.1–26.0)	23.0 (19.3–26.6)	19.2 (15.4–23.0)	21.2 (19.3–23.0)
Day 14	25.6 (19.0–32.1)	31.1 (23.5–38.8)	30.8 (24.9–36.6)	25.9 (19.1–32.6)	28.5 (25.2–32.8)
Day 28	29.0 (19.5–38.6)	35.4 (23.4–47.5)	34.3 (26.6–42.1)	28.6 (20.0–37.3)	32.0 (27.3–36.7)
Doctor visit (95% CI)	7% (2%–20%)	19% (8%–31%)	4% (0.5%–14%)	9% (3%–21%)	9% (6%–14%)
Other medication taken for symptoms (95% CI)	57% (41%–72%)	55% (40%–70%)	55% (39%–68%)	53% (38%–68%)	55% (47%–62%)

* Number of completed cold episodes; 35 participants were counted twice, as they reported two medicated colds. For variables with missing data, numbers of participants who provided information are shown in parentheses. † $P < 0.05$ when compared with the other three treatment groups.
‡ Sum of daily severity scores for individual symptoms (cough, nasal, throat and systemic symptoms), where 1 = mild, 2 = moderate and 3 = severe.

nificantly older than those who did not return cards (45.1 versus 40.9 years; P<0.05), but the two groups did not differ significantly in sex distribution or previous cold history.

Personal characteristics and previous cold history of those who returned cards are shown in Box 2, along with time from symptom onset to beginning medication. Participants in the four medication groups were comparable in sex distribution and time to beginning medication, but those who took Bio C were significantly older and had fewer colds in the previous year than those in the other three groups (P< 0.05).

Cold duration and severity

Duration and severity of symptoms are compared between the four medication groups in Box 2. There were no significant differences between the groups in either mean duration of symptoms or mean severity scores at Days 7, 14 or 28, although the placebo group (30 mg vitamin C daily) had the shortest duration of nasal, systemic and overall symptoms., and the lowest mean severity score at 14 days, and the second lowest at 7 and 28 days.

A box plot of cumulative severity scores at Day 28 (Box 3) revealed that the distribution of values was more dispersed in the 1 g and 3 g vitamin C groups, with the lowest median values occurring in the placebo and Bio C groups. A box plot of cold duration showed a similar pattern (Box 3).

Only 31 participants (17%) recorded a guess about the dose of vitamin C they had taken, and 14 guessed correctly that they had taken a high dose. Seventeen gussed incorrectly that they had taken either a high or low dose.

Actual power of the study

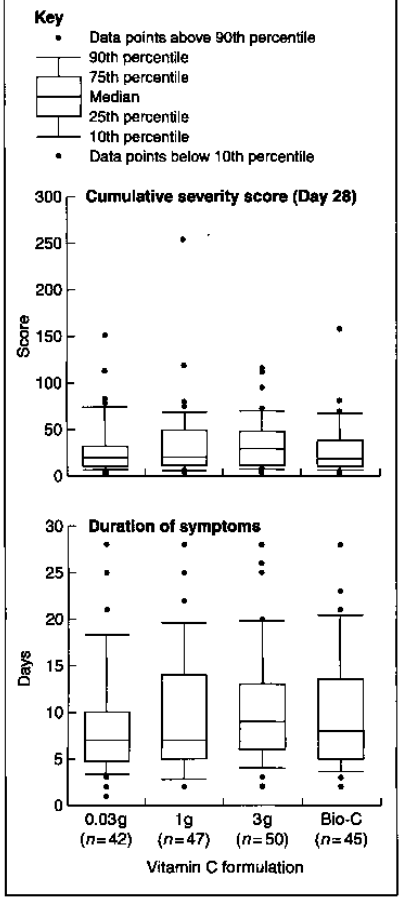
Because the mean cold duration for the whole group was 9.8 days with a standard deviation of 6.6 days, the number of completed cold episodes returned per group provided 80% power to detect a 40% difference in cold duration with a 95% level of confidence. Similarly, given that the mean severity score at Day 28 was 32 with a standard deviation of 32.3, the number of completed cold episodes provided 80% power to detect a 50% difference in severity at the 95% level of confidence.

DISCUSSION

Our study found no significant differences in severity or duration of cold symptoms between groups who took low-dose (placebo) and high-dose vitamin C as treatment for the common cold. The lack of benefit from high-dose therapeutic vitamin C is consistent with the findings of four other randomised controlled trials[2-5] (Box 1).

The Cochrane and other reviews of the published evidence on high-dose vitamin C and the common cold have drawn attention to the relatively consistent trend for those taking *prophylactic*

3: Box plots of cold severity and duration in groups taking different vitamin C formulations



doses in excess of 1 g daily to experience some reduction in duration or severity of colds.[1,7-9] Although high-dose prophylactic vitamin C was also found not to reduce the *incidence* of colds in well-nourished adult populations,[1,7] Hemila has proposed that it may have an effect in groups who are physically stressed or have low nutritional intake.[8-10]

The main weakness of our study is that it necessarily relied on study participants to decide when the criteria for commencing medication were met and to provide all outcome data. In such a study, double-blindness must be rigorously preserved, and allocation to intervention arms must avoid selection bias. We are confident that our study met these requirements and that the few participants who correctly guessed their medication dose did so by chance.

The focus on the university community meant a potential bias in socioeconomic and educational status of participants. The observed spectrum of cold experience may not have been representative of the cold experience of the rest of the Canberra community. Many potential volunteers in our study were ruled ineligible because of their regular use of vitamin C and other, non-traditional approaches for cold therapy and prophylaxis. A recent US study found that 67% of patients seeking medical care for cold episodes believed that vitamin C reduces cold symptoms.[11]

Our target of 75 colds in each treatment group was not reached, despite extension of the study and repeated reminder letters to participants. Fewer than half those enrolled returned a completed respiratory event card. As we expected most to suffer at least one cold during the 18 months of the study, based on their previous history, we assume that many did not use the medication as instructed. Although those who completed a respiratory event card were older than those who did not, both groups had similar previous cold experience. The double-blind nature of the study makes it unlikely that greater compliance would have changed the result.

Our study had medication groups of comparable size, and for each medication group colds were found to have occurred across the entire study period. The Bio-C group was slightly older than the other groups and, probably in consequence, experienced fewer colds in the previous year, as the incidence of colds tends to decrease with age. However, these differences were not associated with significant differences in outcomes.

The average time between symptom onset and medication use was 13 hours, although we encouraged participants to begin medication as soon as four hours after they were certain that a cold was developing. However, the time to beginning medication did not differ significantly between groups.

The power of our study to detect a possible significant difference in symptom severity and duration after high-dose vitamin C treatment was limited by the smaller than expected participation rate. However, the non-significant trend that was observed was the reverse: symptoms tended to be less severe and of shorter duration in the placebo group. The lack of observed benefit in this trial is fully consistent with the observations from the four previous randomised controlled trials that have sought to evaluate this issue.[2-5]

It is time to question again the wisdom and utility of the wide practice of well nourished adults taking mega-doses of vitamin C to treat the common cold, a practice which has become prevalent worldwide since the advocacy of Linus Pauling in the early 1970s.[12,13]

ACKNOWLEDGEMENTS

The project was supported by a grant from Blackmores Ltd, who also provided the study medications. We thank all those who participated in the study for their patience and compliance.

COMPETING INTERESTS

Blackmores Ltd were not involved in conduct or analysis of the trial or preparation of this article.

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(Received 13 Oct 2000, accepted 18 Jun 2001)