INTRODUCTION

Hypovitaminosis C and D are highly prevalent in acute-care hospitals (1–10), but their clinical consequences have rarely been studied (1, 11) and remain almost completely unknown (6). Currently, very few hospitalized patients are prescribed vitamin supplements.

Vitamin C and D play important roles in brain metabolism (12–20). Subclinical vitamin C deficiency induces fatigue and mood disturbance (6), whereas hypovitaminosis D has been linked to cognitive dysfunction (19, 21–25) and depression (16, 26–29). Small randomized clinical trials in the ambulatory setting suggest that vitamin D therapy can improve mental well-being (30, 31) and alleviate depression in people who are vitamin D deficient (29, 32, 33). We observed earlier that appropriate provision of vitamin C improved the mood state of acutely hospitalized patients, whereas vitamin D administration at the upper tolerable dose of 2000 IU/d had no effect (8). No conclusion was possible regarding the benefit of correcting in-hospital hypovitaminosis D insufficiency, however, because the administered dose only slightly increased plasma 25-hydroxyvitamin D [25(OH)D] concentrations during the short time course of the trial (8). The tolerable upper level of vitamin D intake was recently increased to 4000 IU/d (34). Accordingly, we carried out a randomized clinical trial to compare the effects of vitamin C and a very high dose of vitamin D on the psychological well-being of acutely hospitalized patients. The clinical hypothesis was that either vitamin C or high-dose vitamin D administration improves mood and reduces psychological distress in a population of acutely hospitalized patients with a high prevalence of hypovitaminosis C and D.

SUBJECTS AND METHODS

Clinical trial design

The design of the clinical trial was dictated by ethical and practical considerations regarding the use of active treatments compared with inactive placebos. The Canadian government’s Interagency Advisory Panel on Research Ethics requires that, before a placebo control is used in a clinical trial, researchers must provide compelling justification for rejecting other valid methods of achieving internal validity, such as an active treatment control (35). Our previous research in this population indicated that hypovitaminosis C represents a true nutritional deficiency state (6) that can be easily corrected (6) and that such...
the pros and cons of placebo compared with active control sub-
treatment. This use of an active comparison treatment is con-
vitamin D represents a safe and plausible active comparison
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sary burden on the patients and their nurses. Therapy was 500
tables would discourage participation and impose an unnec-
determined that asking patients to take double-dummy placebo
cause the treatment arms were in psychological equipoise, we
decline to participate is the burden of adding more pills to the
study—was that one of the commonest reasons why patients
some patients did make such a determination, it would not bias
administration and immediately pushed into crushed ice in a
light-protected box in which they remained <2 h before being
hand delivered to the research laboratory by one of the inves-
tigators. Immediately after separation in a refrigerated centri-
fuge, plasma samples were deproteinized, flash frozen, and stored
at ≈−80°C and analyzed for reduced ascorbic acid and total vi-
tamin C by electrochemical detection HPLC, as previously de-
described (8). A plasma total vitamin C concentration <28.4 μmol/L
is regarded as vitamin C depletion and a concentration <11.4
μmol/L is regarded as frankly deficient (5, 6). Plasma 25(OH)D
was analyzed by radioimmunoassay (Immunodiagnostic Sys-
tems). A concentration <75 nmol/L is considered subnormal (34).
Intact parathyroid hormone (reference range: 10–70 ng/L) was
measured in plasma by electrochemiluminescence immunoassay
on a Modular Analytics E-Module (Roche). Plasma C-reactive
protein (reference range: 1–10 mg/L) was measured by latex
particle-enhanced immunoturbidimetry on a Cobas Integra 800
analyzer (Roche).

Setting and participants

Over an 8-wk period from 9 June to 3 August 2011, all the
patients on 8 active medical and surgical units of a university
teaching hospital were approached for enrollment if their treat-
ment team approved and they were judged to be mentally com-
petent and fluent in French or English. Patients in the intensive
care unit (or being considered for transfer there) or receiving
renal replacement therapy were not eligible. Eligible patients
were informed that they could be at risk of vitamin C and D
deficiency and invited to participate in the study, which involved
daily administration of vitamin C or vitamin D for a maximum of
10 d. Participating patients were examined for potential signs of
scurvy (skin bruising or hemorrhagic gingivitis), and their BMI
was visually estimated (5, 40).

Randomization and interventions

After enrollment, patients were randomly assigned in pairs to
vitamin C or D therapy by a senior investigator who had no
contact with them. The investigators who enrolled and followed
the patients were blinded as to the treatment assignment. All
the participants were carefully informed, first, of the blinded nature of
the study, and second, that both treatments were active. The
nurses refrained from telling their patients which vitamin was
prescribed. Whereas it is possible that patients could determine
their treatment assignment from the frequency of supplementa-
tion (twice daily for vitamin C, once daily for vitamin D), the
large number of routine medications patients were already being
administered would make such a determination difficult. Even if
some patients did make such a determination, it would not bias
their response because both treatments were active. Our expe-
cience with this patient population—confirmed in the current
study—was that one of the commonest reasons why patients
decide to participate is the burden of adding more pills to the
large number of medications they are already prescribed. Be-
cause the treatment arms were in psychological equipoise, we
determined that asking patients to take double-dummy placebo
tablets would discourage participation and impose an unnec-
mary burden on the patients and their nurses. Therapy was 500
mg vitamin C twice daily or 5000 IU vitamin D once daily for
a maximum of 10 d. This dose of vitamin D slightly exceeded
the tolerable upper level of 4000 IU, but was used because a
single dosage unit was conveniently available. The protocol stip-
ulated that a treatment course was complete if ≥5 d of the 10-d
course of vitamin therapy was completed. Before and after 5–
10 d of vitamin administration, participants completed a mood-
assessment questionnaire, indicated their level of psychological
distress, and had a blood sample drawn for the analyses de-
dscribed below. The study protocol was approved by the Research
Ethics Committee of Montreal’s Jewish General Hospital.

Sample handling and laboratory procedures

Morning fasting blood samples were drawn before any vitamin
administration and immediately pushed into crushed ice in a
light-protected box in which they remained <2 h before being
hand delivered to the research laboratory by one of the inves-
tigators. Immediately after separation in a refrigerated centri-
fuge, plasma samples were deproteinized, flash frozen, and stored
at ≈−80°C and analyzed for reduced ascorbic acid and total vi-
tamin C by electrochemical detection HPLC, as previously de-
described (8). A plasma total vitamin C concentration <28.4 μmol/L
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Analysis of mood and distress

The Profile of Mood States (POMS) is a widely used 65-item
questionnaire that measures mood in healthy, physically ill, and
psychiatric populations; the instrument generates a total mood
disturbance (TMD) score (41–43). The 30-item POMS-B, a briefer
version of the POMS, has been developed to accommodate the
limited reserve of physically ill patients (42, 44, 45). The En-
lish Canadian and Canadian French versions of the POMS-B
(MultiHealth Systems Inc) were used for this study because it is
a validated and widely used broad spectrum tool that can be
administered even to sick, hospitalized patients. TMD scores
range from −20 to 100; higher scores indicate more severe mood
disturbance. The Distress Thermometer (DT) is a validated one-
item measure of psychological distress that directs the patient to
circle a number between 0 and 10 that indicates their level of
distress, alongside an image of a thermometer; a higher score
indicates more intense distress (46, 47). The DT is strongly
recommended as a valid and easy-to-use tool for measuring dis-
trust in people with cancer (46). It was administered at the same
time as the POMS-B. The same investigator carried out each
assessment; neither assessors nor patients knew their treatment
assignment or biochemical vitamin status. Patients completed
the questionnaires by hand or had them read to them without
interference. The assessment was explicitly based on how they
felt on the day of measurement. Initial and final assessments were
always carried out in the same manner and at the same time of
day.
Statistical analysis

The analysis was carried out with GraphPad Prism version 5.04 (GraphPad Software). Descriptive statistics were used to estimate the frequencies, means, and SDs of the study variables. Because the distributions of several variables did not fully meet the criteria for normality, significant differences between unpaired samples were routinely tested for by using the Mann–Whitney U or Fisher’s exact test as appropriate (P < 0.05), and the Wilcoxon’s matched-pairs test was used to detect significant differences in paired comparisons. Except where otherwise indicated, the results are expressed as means ± SDs.

RESULTS

Of the 153 patients considered for enrollment, 88 were mentally competent, were fluent in French or English, understood the nature of the research, signed the informed consent document, and commenced the study; they are referred to as the initial study group (Figure 1). Reasons for declining to participate included an unwillingness to take more pills, mistrust of research, feeling overwhelmed, and fear that vitamins might interact with their ongoing treatment. In this group, 75% of patients had subnormal plasma total vitamin C concentrations, and 30% had frankly deficient concentrations (<11.4 μmol/L); 85% of patients had subnormal plasma 25(OH)D concentrations. Skin bruising was observed in 20 patients and gingival bleeding in 2 patients. The main reasons for withdrawing consent (8 in the vitamin C group, or death (1 in the vitamin C group and 3 in the vitamin D group), or discharge before completing 5 d of therapy (9 in each group), withdrawal of consent (8 in the vitamin C group and 6 in the vitamin D group), or death (1 in the vitamin C group and 3 in the vitamin D group). The main reasons for withdrawing consent were the burden of taking extra pills and undergoing an additional blood test.

The 52 participants in the 2 study completed groups were similar to the initial study group in age, sex, and other variables (Table 1). In particular, 73% had plasma vitamin C concentrations <28.4 μmol/L, 29% had plasma vitamin C concentrations <11.4 μmol/L, and 79% had plasma 25(OH)D concentrations <75 nmol/L. The clinical diagnoses were as follows: solid tumor or hematologic malignancy (46.2% of patients), cardiovascular disease (13.5%), diabetes mellitus (11.5%), infectious disease (17.3%), gastrointestinal disease (17.3%), and other (21.2%). The distribution of these diagnoses was similar in the 2 study completed groups (data not shown). At the time of enrollment, one patient in the vitamin C group had previously been prescribed a daily multivitamin containing 90 mg vitamin C and 400 IU vitamin D, and 2 other patients were prescribed 400 IU vitamin D/d. One patient in the vitamin D group had already been prescribed the same multivitamin, and 3 others were prescribed an average of 1100 IU vitamin D/d.

The patients in the vitamin C group were treated for an average of 8.2 ± 1.8 d (range: 5–11 d). By the end of treatment, their mean plasma total vitamin C concentration increased into the normal range (P < 0.0001; Table 2). Their mean TMD score decreased by 71% from 24.0 ± 18.2 (median and range: 23.5; −10 to 54) to 6.92 ± 14.4 (median and range: 4.5; −20 to 49; P = 0.0002), and their mean DT score decreased by 51% from 4.5 ± 2.9 (median and range: 4.0; 0–9) to 2.2 ± 2.2 (median and range: 2.0, 0–8; P = 0.0002). The patients in the vitamin D group were treated for an average of 8.1 ± 1.7 d (range: 5–11 d). By the end of treatment, their mean plasma 25(OH)D concentration increased by 22% (P < 0.0001) but remained below normal.

Their mean TMD score decreased by 33% from 21.7 ± 17.3 (median and range: 19.0; −9 to 65) to 14.6 ± 17.7 (median and range: 12.0; −12 to 59; P = 0.067), and their mean DT score decreased by 8% from 3.7 ± 2.6 (median and range: 3.5; 1–8) to 3.4 ± 2.8 (median and range: 3.0; 0–8; P = 0.45). Plasma parathyroid hormone concentrations were insignificantly higher in the vitamin C group at baseline and decreased significantly after vitamin C therapy but not after vitamin D therapy (Table 2).

As illustrated in Figure 2, the change in TMD score after vitamin treatment was significantly greater after vitamin C (−17.0 ± 17.8; range: −59 to 11) than after vitamin D (−7.1 ± 18.2; range: −58 to 26; P = 0.045). Similarly, the change in DT score was significantly greater after vitamin C (−2.3 ± 2.3; range: −6 to 1) than after vitamin D (−0.35 ± 2.7; range: −6 to 7; P = 0.009).

In a secondary analysis, we tested the hypothesis that beneficial changes in mood and distress were related on an individual basis to changes in plasma total vitamin C concentrations in all 52 patients. The correlation between improvement in TMD score and increase in plasma total vitamin C concentrations was significant (Spearman P = 0.0025), whereas the correlation between reduction in distress and increase in plasma total vitamin C was nearly significant (Spearman P = 0.064).

DISCUSSION

This clinical trial was carried out to determine whether an improvement in mood after vitamin C (but not vitamin D) therapy observed in a previous trial (8) would be reproduced in a new clinical trial that enrolled more participants, used 2 different
TABLE 1
Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial study group (n = 88)</th>
<th>Vitamin C (n = 26)</th>
<th>Vitamin D (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>64.5 ± 15.4</td>
<td>65.5 ± 15.4</td>
<td>67.0 ± 14.1</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>53.4</td>
<td>57.7</td>
<td>50.0</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>13.6</td>
<td>7.7</td>
<td>23.1</td>
</tr>
<tr>
<td>Time in hospital at enrollment (d)</td>
<td>16 ± 23</td>
<td>15 ± 21</td>
<td>12 ± 11</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>72.4 ± 17.0</td>
<td>70.0 ± 14.8</td>
<td>73.5 ± 18.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 ± 5.7</td>
<td>25.3 ± 5.0</td>
<td>25.6 ± 5.7</td>
</tr>
<tr>
<td>Blood hemoglobin (g/L)</td>
<td>108 ± 18.3</td>
<td>109 ± 17.1</td>
<td>108 ± 13.6</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>32.0 ± 7.1</td>
<td>32.2 ± 6.9</td>
<td>31.5 ± 6.9</td>
</tr>
<tr>
<td>Plasma ascorbic acid (µmol/L)</td>
<td>60.3 ± 74.1</td>
<td>74.9 ± 97.0</td>
<td>39.0 ± 44.2</td>
</tr>
<tr>
<td>Plasma parathyroid hormone (ng/L)</td>
<td>44 ± 42</td>
<td>52 ± 66</td>
<td>36 ± 23</td>
</tr>
<tr>
<td>Plasma ascorbic acid (µmol/L)</td>
<td>20.6 ± 17.3</td>
<td>21.0 ± 17.4</td>
<td>18.7 ± 13.7</td>
</tr>
<tr>
<td>Plasma total vitamin C (µmol/L)</td>
<td>23.6 ± 19.6</td>
<td>25.6 ± 22.3</td>
<td>21.7 ± 15.6</td>
</tr>
<tr>
<td>Patients with subnormal values (%)</td>
<td>75</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>Plasma 25-hydroxyvitamin D (nmol/L)</td>
<td>51 ± 22</td>
<td>52 ± 24</td>
<td>54 ± 24</td>
</tr>
<tr>
<td>Patients with subnormal values (%)</td>
<td>85</td>
<td>81</td>
<td>77</td>
</tr>
<tr>
<td>Total mood disturbance score</td>
<td>21.1 ± 18.7</td>
<td>24.0 ± 18.2</td>
<td>21.7 ± 17.3</td>
</tr>
<tr>
<td>Distress Thermometer score</td>
<td>3.7 ± 2.7</td>
<td>4.5 ± 2.9</td>
<td>3.7 ± 2.6</td>
</tr>
</tbody>
</table>

1 There were no significant differences between the initial study group and the study-completed group as a whole or between the vitamin C and vitamin D groups with the Mann-Whitney U test or Fisher’s exact test for categorical values.
2 Mean ± SD (all such values).
3 Reference ranges are as follows: albumin (35–50 mg/L), parathyroid hormone (10–70 ng/L), C-reactive protein (<10 mg/L), hemoglobin (120–150 g/L), total vitamin C (>28.4 µmol/L), and 25-hydroxyvitamin D (75–250 nmol/L).
4 Total vitamin C is the sum of ascorbic acid and dehydroascorbic acid.
5 The total mood disturbance score ranges from 0 to 100.
6 The Distress Thermometer score ranges from 0 to 10.

TABLE 2
Metabolic and psychological effects of vitamin C and D therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vitamin C–treated patients (n = 26)</th>
<th>Vitamin D–treated patients (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>Plasma ascorbic acid (µmol/L)</td>
<td>21.0 ± 17.4</td>
<td>69.1 ± 34.9</td>
</tr>
<tr>
<td>Plasma total vitamin C (µmol/L)</td>
<td>25.6 ± 22.3</td>
<td>79.5 ± 39.1</td>
</tr>
<tr>
<td>Plasma 25-hydroxyvitamin D (nmol/L)</td>
<td>52 ± 24</td>
<td>54 ± 26</td>
</tr>
<tr>
<td>Plasma C-reactive protein (mg/L)</td>
<td>74.9 ± 97.0</td>
<td>50.9 ± 71.3</td>
</tr>
<tr>
<td>Plasma parathyroid hormone (ng/L)</td>
<td>52 ± 66</td>
<td>38 ± 28</td>
</tr>
<tr>
<td>Total mood disturbance score</td>
<td>24.0 ± 18.2</td>
<td>6.9 ± 14.4</td>
</tr>
<tr>
<td>Distress Thermometer score</td>
<td>4.5 ± 2.9</td>
<td>2.2 ± 2.2</td>
</tr>
</tbody>
</table>

1 All values are means ± SDs.
2 Details about the variables and their reference ranges are shown in Table 1.
3 Wilcoxon’s matched-pairs test.
deficiency or to a more general improvement in physiologic function.

Second, the clinical trial has internal validity. Baseline and posttreatment vitamin status were determined by using rigorous procedures for sample handling, storage, and analysis—important strengths that are lacking in most nutritional intervention studies (51). The 2 different, validated, and widely used instruments for measuring psychological well-being were in close agreement as to the direction and magnitude of the treatment effect. The characteristics of the patients who completed treatment were similar to the ones who began the study, and the comparison groups who completed the study were similar to one another (Table 1), including in their diagnostic mix, length of hospital stay at the time of enrollment, and duration of treatment. Some dropout is inevitable with in-hospital pragmatic clinical trials. It was prespecified in the protocol that a treatment was complete if 5 d of therapy were completed. The number of patients who did not complete 5 d of treatment was small in relation to the number enrolled and similar in number and reason in the 2 treatment groups, the most frequent reason being early discharge from hospital. It is unlikely, therefore, that participant dropout or another source of internal bias could have distorted the results enough to account for the large differences in outcome between the 2 treatment arms.

In addition, the large improvements in psychological well-being in the vitamin C–treated patients could not be explained by improvements in their general clinical condition. When untreated, hypovitaminosis C persists indefinitely in hospitalized patients (5), and any improvement in general clinical condition would not be restricted to the vitamin C group, unless correction of vitamin C deficiency itself caused a general physiologic improvement.

This pragmatic clinical trial also has external validity. The participants were typical of the heterogeneous mix of patients admitted to modern tertiary acute care hospitals, and the treatment was simple, safe, and applicable to everyday clinical practice (52, 53). The high prevalence of hypovitaminosis C among these patients, and the large magnitude of the beneficial effect of correcting it, makes these findings highly clinically relevant because alleviation of distress is a major goal of patient-centered care (46, 54, 55).

It is of potential interest that baseline plasma parathyroid hormone concentrations, which were modestly but insignificantly higher at baseline in the vitamin C group, decreased after vitamin C (but not after vitamin D) therapy (Table 2). We cannot explain this observation. In our view the higher baseline parathyroid hormone concentration in this group is most likely a chance finding with subsequent regression to the mean. Nonetheless, it is of some interest, because plasma vitamin C and parathyroid hormone concentrations are seldom measured together. An inverse association between them has been reported in hemodialysis patients (56), and preliminary evidence suggests that vitamin C therapy reduces parathyroid hormone concentrations in these patients (57).

This study had several weaknesses. It was relatively small and hence needs to be replicated in other centers (58). Small trials can be valuable when they test a novel important question, are carefully designed and executed, and the treatment effect is large, robust, and clinically relevant (59). The 71% improvement in mood disturbance after vitamin C therapy is similar to our observations in 2 earlier clinical trials that involved the same treatment in precisely similar patients (6, 81). Importantly, it remains to be determined whether the beneficial effects of normalizing vitamin C status last beyond the 5–10-d duration of this clinical trial.

Finally, it may be considered a weakness that, when the study was designed, the authors failed to adequately consider the possibility that the chosen dose of vitamin D, even though greater than the tolerable upper limit (34), would be insufficient to increase plasma 25(OH)D concentrations into the normal range within 5–10 d. Because of this design weakness, no conclusion is possible regarding the potential effectiveness of vitamin D therapy in hospitalized patients with hypovitaminosis D. The biological half-life of vitamin D appears to be long and variable (60, 61). Our results confirm what other recent reports (62–64) also indicate, namely, that several weeks of continuous high-dose vitamin D therapy would be necessary to normalize plasma 25(OH)D concentrations in this population. These findings strongly suggest the merit of developing and validating a safe and effective ultrahigh vitamin D loading and maintenance dose protocol for situations in which prompt clinical improvement is deemed to be in the patient’s interest (64–66).

In conclusion, this research confirms several earlier reports that document an extremely high prevalence of hypovitaminosis C and D in acutely hospitalized patients. Because this information has been restricted almost entirely to nutrition journals, it remains
unknown to most physicians. In this randomized clinical trial, vitamin C administration normalized plasma vitamin C concentrations and substantially reduced mood disturbance and psychological distress in acutely hospitalized patients—a novel finding with important clinical implications in light of the goals of patient-centered care. No conclusion can be drawn regarding the potential benefits of vitamin D therapy in this patient population. Because of its long and variable half-life, future clinical trials of in-hospital vitamin D therapy will require the development and validation of a safe and effective ultrahigh loading dose protocol.

We are indebted to the physicians, dietitians, and nurses of the Jewish General Hospital for their generous assistance.

The authors’ responsibilities were as follows—SE, EM, and LJH: carried out the blinded randomization; YW and XJL: acquired the data; LR: analyzed the data and carried out the statistical analysis; and YW and LJH: drafted the manuscript. All authors were involved in the study concept and design and in the revision of the manuscript. None of the authors had a financial disclosure.

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