The Effect of Curcumin in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis Disparate Responses in Different Disease Severities

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Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), is a chronic and often disabling disease. Although the exact pathophysiological mechanism of ME/CFS is unknown, immunological abnormalities may play an important role. Curcumin is an herb with powerful anti-oxidative and anti-inflammatory properties. Therefore, we hypothesized that curcumin would have favorable effects on symptomatology in ME/CFS patients. In an open trial among 65 ME/CFS participants, 6 stopped the use of curcumin because of side effects and 8 did not complete the end of study questionnaire. Before and after the use of curcumin complexed with phosphatidyl choline, -500 mg bid, participants completed the CDC inventory for assessment of Chronic Fatigue Syndrome. The CDC questions (n=19) were scored and divided into 2 parts: the first being specific for CFS complaints (n=9), the second being scores of less specific symptoms (n=10); denoted as CDC other score. Results showed that 8 weeks of curcumin significantly decreased the CDC CFS-related symptom scores and CDC other scores, especially in patients with mild disease. Conclusion: In this open-labeled study 8 week curcumin use in a phosphatidyl choline complex reduced ME/CFS symptomatology, especially in patients with mild disease severity.

Keywords: Curcumin, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Disease severity, CDC score, Fukuda score, R and 36 questionnaire.

Introduction

Curcumin is an herb with powerful anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-microbial properties [1-9]. Oxidative stress can lead to chronic inflammation. Curcumin can decrease TNF-a production and can inhibit inflammatory cytokines. See for extensive reviews the studies of Pulido-Moran [10-20].

Because of these properties, curcumin has been studied in inflammatory diseases in lungs, joints, bowels, brains, and the cardiovascular system, rheumatoid arthritis, inflammatory bowel disease, Alzheimer’s disease, mood disorders, cancer, diabetes, pain. Although animal Experimental studies are overwhelmingly positive, there is only limited data from human studies [21-27].

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), is a chronic and often disabling disease. The exact prevalence is unknown but estimates in the US vary between 836,000 and 2.5 million patients, in the Netherlands between 20,000 and 80,000 patients. Patients with ME/CFS have been found to be more functionally impaired than those with other disabling illnesses [28-30].

Although the exact pathophysiological mechanism of ME/CFS is unknown, immunological abnormalities may play an important role. Oxidative stress is increased in ME/CFS patients. The data on cytokines are contradictory and a recent meta-analysis showed no overall change for approximately 80 plasma cytokines studied in ME/CFS patients compared to controls. We previously showed in an open treatment trial that curcumin has favorable effects on symptomatology in ME/CFS patients, possibly because of the anti-oxidative and anti-inflammatory properties of curcumin. In the present study we hypothesized that effects in patient reported outcomes might be dependent on the severity of the disease [31-37].

Patients and Methods

Patients with ME/CFS were asked to participate in the registry and gave informed consent. All fulfilled the Fukuda criteria for CFS and the ME criteria. Disease severity was scored according to the ME criteria as mild, moderate, or severe. For this analysis, patients with moderate and severe disease severity were grouped together and compared with those who had mild disease [38,39].

Patients were asked to complete the CDC inventory for assessment of Chronic Fatigue Syndrome, Dutch language version, prior to the start of using curcumin and return the questionnaire by mail or email. After 8 weeks of curcumin use, the same questionnaire was completed. Prior to the start of curcumin they also completed the SF-36 questionnaire [40-42]. Patients used Curcumin Phytosome (Curcuma longa extract complexed with phosphatidylcholine; NOW®) 500 mg capsules twice a day. According to the
manufacturer the capsules contained at least 18% (90 mg) curcuminoids.
In total 65 patients participated. Six patients stopped the use of curcumin because of side effects (all of gastro-intestinal origin). Eight patients did not return the second questionnaire despite two reminders. These 14 participants were excluded from the analysis, leaving 51 participants with complete data. No other treatments for ME/CFS were used during this study period. No side-effects were reported in the patients who completed the trial period and returned the second questionnaire. The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The medical ethics committee of the Slotervaart Hospital, Amsterdam, NL, approved the use of patient data for research (code U17.089/P1736).

Data analysis
The CFS CDC inventory contains 19 symptom questions and collects information about the presence, frequency, and intensity of 19 illness-related symptoms during the month preceding the interview; these symptom questions include all the CFS-defining symptoms. Perceived frequency of each symptom was rated on a five-point scale (0-4) and severity or intensity of symptoms was measured on a four-point scale (0-3). Individual symptom scores were calculated by multiplying the frequency score by the intensity score. For this purpose the intensity scores were transformed into equidistant scores (0, 1, 2.5, and 4) before multiplication. This results in a range of 0–16 for each symptom [40].

The CDC score contained the summed score of the 19 symptoms. For the purposes of this analysis, we subdivided the CDC score into 2 parts: the CFS score and the CDC other score. The CFS score consisted of the 8 CFS defining symptoms namely, post-exertional fatigue, unrefreshing sleep, problems remembering or concentrating, muscle aches and pains, joint pains, sore throat, tender lymph nodes and headaches. In the CFS diagnostic criteria memory and concentration difficulties are taken as one combined symptom, whereas in the CDC inventory these 2 symptoms are scored separately. Therefore, for the CFS scores 9 symptoms were summed. The 10 remaining CDC questions that were not related to the CFS score were also summed and labeled as CDC-Other score. The CDC other score is composed of the symptoms: diarrhea, fever, chills, sleep problems, nausea, stomach or abdominal pain, sinus or nasal problems, shortness of breath, light hypersensitivity and depression.

Moreover, in the second, post-curcumin questionnaire, we asked how you rate your global physical and mental condition after using curcumin: 0: strongly deteriorated, 1: mildly deteriorated, 2: no change, 3: mildly improved and 4: strongly improved. One patient reported mild deterioration after curcumin use. For the chi-square analysis this Patient was added to the no change group. Similarly, the two improvement answers were also analyzed together.

Statistical Analysis
Scores were tested for normal distribution using the Shapiro-Wilk test in SPSS (IBM SPSS version 21). Normally distributed data are presented as mean (SD) and non-normally distributed data as median (IQR).

Data were compared with Student’s t-test for paired and unpaired data, and with the Mann-Whitney U test for non-normally distributed data, where appropriate. Chi square analysis was performed on the distribution of the Patient Reported Outcome Measure (PROM): yes or no change in physical and mental condition after curcumin use. A p value <0.05 was considered significantly different.

Results
Table 1 shows the demographic data for the 51 participants analyzed. Forty-two females and 9 males were included. The mean disease duration was 16 (9) years, and the mean age was 47 (11) years. Except for height and weight, there were no differences between males and females (data not shown).

According to the ME criteria 26 patients were graded as mild and 25 as moderate to severe (15 moderate and 10 severe patients). Table 1 also shows the baseline data for the mild vs the combined moderate and severe group. No differences were present except for the SF-36 physical functioning scale; as expected, mildly affected patients had a higher physical functioning scale than the moderately and severely affected patients p<0.0001.

Table 1: Baseline characteristics of the total group and of the mild vs the moderate to severe ME/CFS patients.

<table>
<thead>
<tr>
<th></th>
<th>Total Group</th>
<th>Mild</th>
<th>Moderate/Severe</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>51</td>
<td>26</td>
<td>25</td>
<td>ns</td>
</tr>
<tr>
<td>Male/Female</td>
<td>9/42</td>
<td>7/19</td>
<td>2/23</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47 (11)</td>
<td>48 (11)</td>
<td>45 (11)</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of ME/CFS</td>
<td>16 (9)</td>
<td>15 (9)</td>
<td>16 (9)</td>
<td>ns</td>
</tr>
<tr>
<td>Height</td>
<td>173 (8)</td>
<td>174 (8)</td>
<td>172 (7)</td>
<td>ns</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 (16)</td>
<td>73 (14)</td>
<td>68 (17)</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5 (4.1)</td>
<td>24.1 (3.4)</td>
<td>22.9 (4.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>134 (16)</td>
<td>138 (14)</td>
<td>130 (16)</td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>81 (8)</td>
<td>82 (8)</td>
<td>79 (8)</td>
<td>ns</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>74 (13)</td>
<td>73 (10)</td>
<td>75 (15)</td>
<td>ns</td>
</tr>
<tr>
<td>SF-36 physical functioning scale (%)</td>
<td>50 (26)</td>
<td>72 (13)</td>
<td>29 (15)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 2: CDC inventory score results and the PROM: the change in physical and mental condition after curcumin use.

<table>
<thead>
<tr>
<th></th>
<th>Total Group</th>
<th>Mild</th>
<th>Moderate/Severe</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>51</td>
<td>26</td>
<td>25</td>
<td>ns</td>
</tr>
<tr>
<td>CDC score base</td>
<td>91.8 (39.9)</td>
<td>81.2 (35.2)</td>
<td>102.7 (42.4)</td>
<td>ns</td>
</tr>
<tr>
<td>CDC score post</td>
<td>80.0 (40.9)</td>
<td>60.3 (24.4)</td>
<td>100.5 (45.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CFS score base</td>
<td>59.3 (25.5)</td>
<td>53.1 (20.9)</td>
<td>65.7 (29.0)</td>
<td>ns</td>
</tr>
<tr>
<td>CFS score post</td>
<td>51.4 (25.6)</td>
<td>40.6 (17.5)</td>
<td>62.6 (27.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CDC other score base</td>
<td>32.5 (20.0)</td>
<td>28.1 (20.3)</td>
<td>37.0 (19.5)</td>
<td>ns</td>
</tr>
<tr>
<td>CDC other score post</td>
<td>28.6 (18.6)</td>
<td>19.7 (10.1)</td>
<td>37.8 (21.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PROM: Improvement</td>
<td>18 (35%)</td>
<td>13 (50%)</td>
<td>5 (20%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PROM: Unchanged</td>
<td>33 (65%)</td>
<td>13 (50%)</td>
<td>20 (80%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

PROM = patient reported outcome measures of physical and mental condition change after curcumin use.

**Discussion**

To the best of our knowledge, this is the first study that indicates that curcumin use has a positive effect on symptoms in ME/CFS patients as assessed by the CDC inventory for CFS, and that those with more severe disease are less likely than those with mild disease to report improvement. In 2018 we published the first open label results in ME/CFS patients, showing curcumin might be a supplement to be prescribed in ME/CFS patients [van Campen 2018]. In this larger group we investigated whether there was a relation between disease severity and efficacy.

Symptoms in ME/CFS include a perpetual flu-like state, sore throats, tender/swollen lymph nodes, muscle pain, achy joints without swelling or redness, headaches, chills, “feverishness” and sensitivities to foods, odors, and medications, which are all indicative of inflammation [28]. As increased oxidative stress and altered cytokine patterns have been demonstrated in ME/CFS, it is likely that curcumin exerts its beneficial effects by the anti-oxidative and anti-inflammatory properties. However, the exact mode of action of curcumin needs to be determined. Moreover, ME/CFS is considered to be in part a neuro-inflammatory disease as curcumin passes the blood-brain barrier it is therefore tempting to assign the positive effects also to an anti-oxidative and anti-inflammatory effect in the brain [1-6,31-36,43-49].

Overall, the effect of curcumin use on ME/CFS symptoms is limited: for the total ME/CFS patient group the total CDC score decreased from 91.8 (39.9) to 80.0 (40.9), a mean reduction of 12% (data not shown). The limited efficacy is also obvious from the PROM: change in physical and mental condition after curcumin use. Thirty-five percent of patients reported improvement in their physical and mental condition after curcumin use. The finding that the PROM: improved is associated with a larger decrease in the total CDC score strengthens the validity of this study.

A difference in treatment efficacy was found between patients with mild disease versus moderate or severe disease. In the latter group curcumin was less effective. This observation is not uncommon in other diseases. For example, in a study using a bronchodilator for COPD (Chronic Obstructive Pulmonary Disease), the medication under study was less effective in severe COPD vs moderate COPD [50]. The reduced efficacy in the moderate to severe ME/CFS patient group may be related to a higher load of inflammation in this patient group in combination with the low bioavailability of curcumin. In the unprocessed form the uptake of curcumin is very low. To improve uptake, encapsulation in liposomes, polymeric nanoparticles, cyclodextrin encapsulation, lipid complexes, phosphatidylcholine complexes or polymer-curcumin complexes have been developed, all of which increase the activity and bioavailability. In a study the absorption of a standardized curcuminoid mixture and its lecithin formulation was compared [19,51,52].

Total curcuminoid absorption was about 29-fold higher than for its corresponding unformulated curcuminoid mixture, but plasma concentrations were still significantly lower than those required for the inhibition of most anti-inflammatory targets of curcumin. Remarkably, the phospholipid formulation increased the absorption of demethoxylated curcuminoid much more than that of curcumin, being a more potent analogue in many in vitro anti-inflammatory assays. It is possible that an even higher dose or an increased bioavailability of curcumin and or demethoxylated curcuminoid may be more effective in moderate to severe ME/CFS patients. These needs to be studied and further efforts to increase bioavailability and the clinical effects of the different curcuminoid components are also needed.

An interesting finding was that not only the CFS score decreased significantly in the mild disease group, but also the CFS-other scores. Some of these symptoms might be related to inflammation and therefore might respond to curcumin treatment. A larger study is needed to confirm these results.

**Figure 1:** Difference in post and pre-treatment CDC score in ME/CFS patients with deterioration or no change and ME/CFS patients with improvement after 8 weeks of treatment with curcumin (panel A), difference in CFS score in ME/CFS patients with deterioration or no change and ME/CFS patients with improvement after 8 weeks of treatment with curcumin (panel B) and difference in CDC rest score in ME/CFS patients with deterioration or no change and ME/CFS patients with improvement after 8 weeks of treatment with curcumin (panel C).

Table 2 also shows the differences between patients with mild disease vs moderate and severe disease. Baseline CDC, CFS and CDC other scores were all higher in the mildly affected patients versus the moderate and severe patients, but did not reach statistical significance. After 8 weeks of curcumin use, both the total CDC scores, the CFS scores and CDC other scores were significantly lower (p<0.001, p<0.01 and p<0.001 respectively), compared to pre-curcumin use in the mild ME/CFS group, but were not different in the moderate to severe ME/CFS group.

**Figure 1:** Shows the changes in CDC, CFS and CDC other scores with respect to the patient reported outcome of neutral/deterioration or improvement. **Figure 2** shows the pre- and post-treatment values of the three scores in both mild versus moderate to severe ME/CFS patients. The CDC, CFS, and CDC other scores post curcumin use were all significantly lower in the mild ME/CFS group, whereas not different in the moderate to severe ME/CFS group. In the group with mild disease (n=26) 13 reported improvement in the global physical and mental condition, 13 reported no change. In the moderate/severe group, 5 reported improvement and 20 reported no change (p<0.05).

**Figure 2:**CDC score pre and post treatment in mild and moderate/severe ME/CFS patients (panel A), CFS score pre and post treatment in mild and moderate/severe ME/CFS patients (panel B) and CDC rest score pre and post treatment in mild and moderate/severe ME/CFS patients (panel C).

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needed to address the question regarding which specific symptoms are ameliorated by curcumin. Unexpectedly, a relatively high number of ME/CFS patients (n=6, 10%) stopped the use of curcumin because of side effects. The explanation may be that multiple chemical sensitivities are prevalent in ME/CFS patients. In the study of Brown and Jason, the co-occurrence was almost 24% [53]. It is unclear whether the drug itself or added excipients cause the intolerance. The patients completing the study reported no side effects due to this supplement. The meta-analysis of reported nausea and gastro-intestinal side effects to be the main reported adverse events. They also reported studies showing no any side effects. The ME/CFS patients with side effects found these severe enough to stop the treatment [54].

Limitations
This study was an open-label study, without a placebo arm. Some patients (n=8) did not return the first or second questionnaire, possibly leading to bias. A number of patients in the outpatient clinic admitted that they had difficulties with completing the questionnaire. This is most probably due to their memory and concentration problems, a disabling feature of the disease. A supervised completion approach may overcome this problem. The meta-analysis of table 1 shows an overview of trials in which there were different doses and durations of treatment, varying from single dose interventions up to treatment durations of 22 months [54]. We chose – empirically in the ME/CFS patient group – for treatment duration of 8 weeks. If a positive response is not present after 8 weeks, the likelihood that improvement will occur with longer duration is considered to be low. As patients are not reimbursed for the intolerance. The patients co-

Conclusion
In summary, in this open-labeled study, 8 weeks of curcumin use in a phosphatidylcholine complex reduced ME/CFS symptomatology, especially in patients with mild disease, whereas it did not significantly change symptoms in moderate and severe patients. A randomized placebo-controlled, larger study is warranted to assess its efficacy in ME/CFS patients.

Data Availability Statement
The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

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References
