

Spirulina did not Ameliorate Idiopathic Chronic Fatigue in four N-of-1 Randomized Controlled Trials

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Abstract

Idiopathic chronic fatigue is an exclusion diagnosis established when no chronic disease is found. *Spirulina platensis* is an alga with a rich content of proteins, vitamins, minerals and amino acids and is considered as a bioactive additive with multiple effects, among them being effects against fatigue. However, despite the worldwide utilization of *Spirulina*, there are only a few quality studies with it and none concerning fatigue. The Nof- 1 randomized trials are made on one patient, and by this kind of study the efficacy of a treatment on that particular patient can be assessed. A series of four N-of-1 double-blind, randomized trials were performed on four physicians who complained of chronic fatigue. Each patient was his own control and received three pairs of treatments comprising 4 weeks of spirulina and 4 weeks of placebo. *Spirulina platensis* was administered in a dose of 3 g/day. For each pair, the order of treatments was randomized. Outcome measures were severity of fatigue measured on a 10-point scale.

The scores of fatigue were not significantly different between spirulina and placebo.

Spirulina administered in a dose of 3 g/day did not ameliorate fatigue more than the placebo in any of the four subjects, and possibly it has no effect on chronic fatigue. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: spirulina; N-of-1 trial; single-case research; randomization; double-blind.

INTRODUCTION

The term spirulina refers to a large number of cyanobacteria, or blue-green algae, which are a rich source of nutrients, containing up to 70% protein, B-complex vitamins, phycocyanin, chlorophyll, betacarotene, vitamin E and numerous minerals (Cifferi, 1983). Spirulina has

been said to possess a variety of medical uses. However, these uses have not been thoroughly studied in humans, and there is limited scientific evidence about safety or effectiveness. Scientists have studied spirulina for the following health problems: high cholesterol (Ionov and Basova, 2003; Samuels *et al.*, 2002), diabetes (Mani *et al.*, 2000), oral leucoplakia (Mathew *et al.*, 1995), chronic viral hepatitis (Baicus and Tanasescu, 2002) and malnutrition (Branger *et al.*, 2003).

Fatigue is a common complaint, which may account for up to 37% of patients presenting to family physicians with general weakness or tiredness for any length of time (Okkes *et al.*, 2002). One of the indications of *Spirulina*, claimed by numerous manufacturers, is idiopathic chronic fatigue. Because of the lack of evidence and based on mixed anecdotal reports, it was decided to perform N-of-1 trials on four of our colleagues who complained of chronic fatigue. One of them was a resident who had taken spirulina previously for fatigue and had reported beneficial effects.

The N-of-1 trials are randomized controlled trials (RCTs) in individual patients. Built on the work of experimental psychologists with single-case or single-subject research, they maintain the methodological safeguards provided by RCTs (Portney and Watkins, 1993; Guyatt *et al.*, 1986). Because they determine the best care for the particular patient of interest, without issues of external validity, they were situated recently at the top of the hierarchy of strength of evidence for treatment decisions, above systematic reviews of randomized trials (Guyatt *et al.*, 2002a).

METHODS

Each subject received three pairs of treatments starting in March 2004. Each pair consisted of a 4 week period of *Spirulina platensis* treatment (1 g t.i.d.) and a 4 week period of placebo treatment (Fig. 1). For each pair of treatments the order of spirulina and placebo was randomized. The random sequence was prepared in advance by one of the investigators for each subject separately. Only that investigator (who did not participate in the assessment of the subjects) was aware of the sequence of treatments. Identical capsules of similar colour, smell and taste were used to ensure blinding. Washout periods were interpolated between the periods of treatment in order to avoid the carry-over effects. Because no information, either in the literature or in the package insert, was found concerning the amount of time necessary for the full effect and/or cessation of action once stopped, durations were chosen that were considered long enough for the treatment (1 month) and for the wash-out (2 weeks).

To eliminate carry-over effects, fatigue was measured only during the second half (weeks 3 and 4) of the 'treatment' periods.

The measured outcome was fatigue, self-evaluated by every subject on a ten-point scale (0 – severe fatigue, 10 – no fatigue). Because subjects 1 and 2 complained of matinal (wake-up), and postprandial fatigue, respectively, they evaluated their type of fatigue. The others evaluated fatigue for the whole day. Every subject kept a diary where he marked the score daily, during the second half of each ‘treatment’ period (either spirulina or placebo). Because the single case design was used, all outcome measures were analysed for each patient separately. The subjects recorded 14 scores for every ‘treatment’ period, for which the mean score was calculated. At the end of the trial, there were three pairs of mean scores (Table 1) which were analysed, as indicated by other authors (Sackett *et al.*, 1991; Guyatt *et al.*, 2002b), with a Student’s paired *t*-test. GraphPad InStat 3.06 for Windows was utilized for statistics (GraphPad Software, Inc., San Diego California USA, www.graphpad.com). The difference was considered significant when $p < 0.05$.

RESULTS

Four N-of-1 randomized trials were made on four physicians (a specialist and three residents) who complained of idiopathic chronic fatigue. The subjects had no organic disease and did not fulfil the criteria for depression or chronic fatigue syndrome. They did not take any concomitant medication. Their ages were 40, 31, 29 and 28 and they were three men and a woman. All the subjects completed the 36 week trial. None of the subjects reported any side effect.

The fatigue scores are summarized for every patient as box-plot graphs in Figs 2–5. As can be seen by visual inspection, there did not appear to be a difference between spirulina and placebo in any of the four patients.

The mean scores for the treatment periods are given in Table 1. No significant difference between spirulina and placebo concerning the fatigue score ($p > 0.05$, Table 1) was found.

As a result, the resident who used to take spirulina before the trial discontinued its use.

DISCUSSION

Spirulina platensis administered in a dose of 3 g/day did not ameliorate fatigue more than placebo in any of the four subjects. Spirulina is produced and sold worldwide. In Romania it is both produced locally and imported, and it is expensive.

Spirulina is a nutritive supplement which, based on theory and tradition, is supposed to have multiple beneficial effects. However, most have not been proven by quality clinical studies, the great majority of the studies being of grade C of evidence (unclear scientific evidence for this use) and even grade D (fair scientific evidence against this use).

One of the unproven indications of spirulina is idiopathic chronic fatigue, and we proceeded to this series of four N-of-1 randomized trials, at the end of which it was concluded that, in the four subjects, spirulina did not ameliorate fatigue.

There is no other study concerning the utilization of spirulina in idiopathic chronic fatigue. In fact, this is one of the indications for N-of-1 studies (Sackett *et al.*, 1991): without any previous valid research, the effectiveness of spirulina in chronic fatigue was in doubt.

Spirulina was not efficient for the treatment of idiopathic chronic fatigue in our subjects. However, it might be efficient in other patients. Apart from this study, there is no valid proof that spirulina might be efficient for chronic fatigue in any subject. In order to demonstrate this, the producers should conduct RCTs.

Acknowledgement

Hofigal SA Bucharest furnished the medication and placebo.

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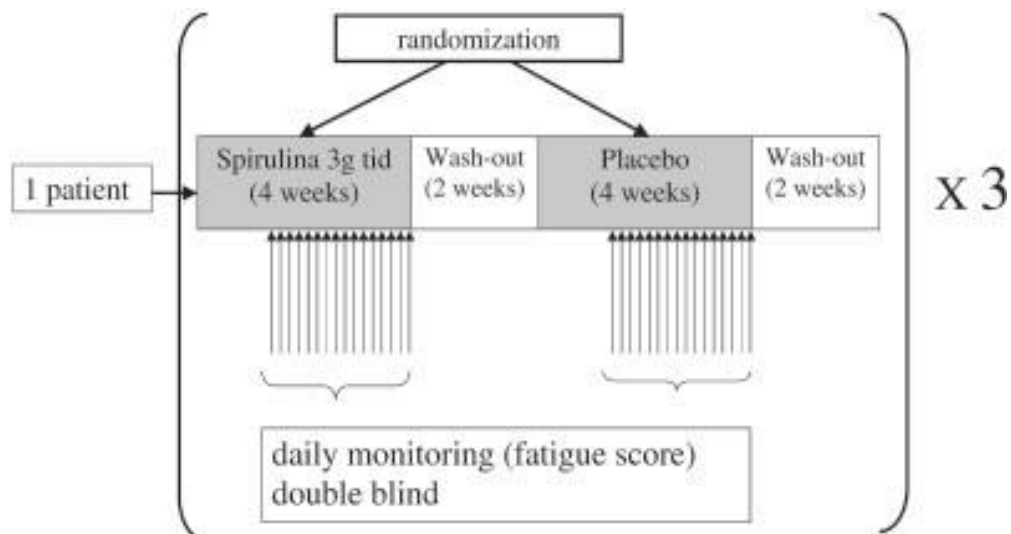


Figure 1. Study design

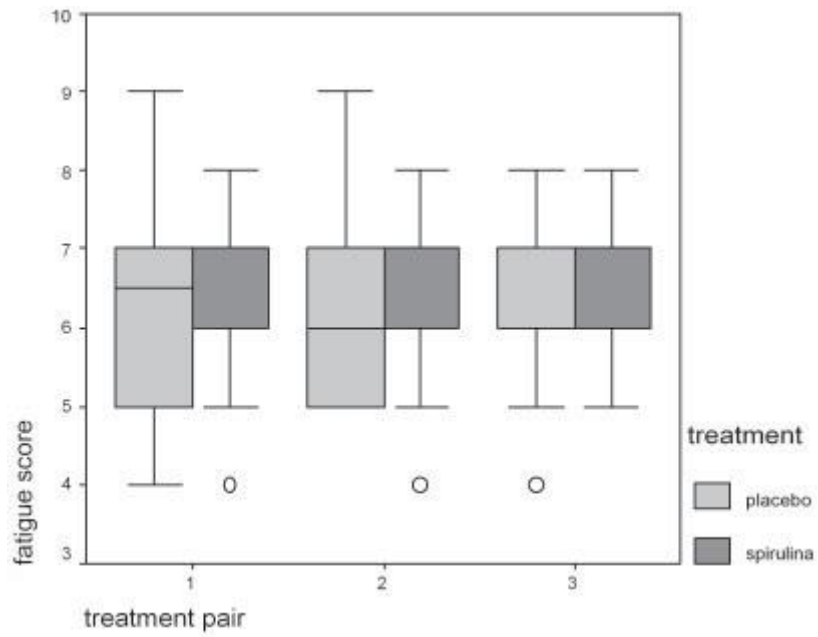


Figure 2. Fatigue scores evolution in patient 1.

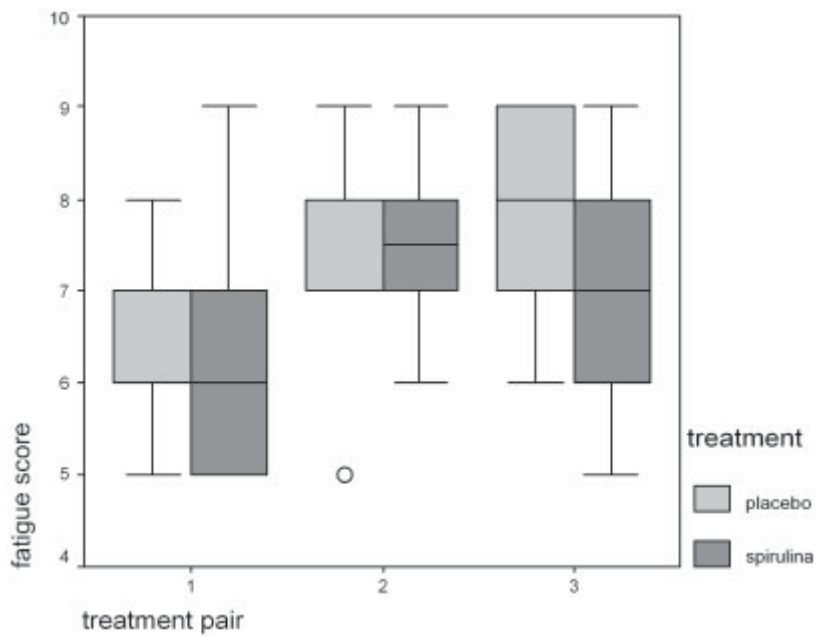


Figure 3. Fatigue scores evolution in patient 2

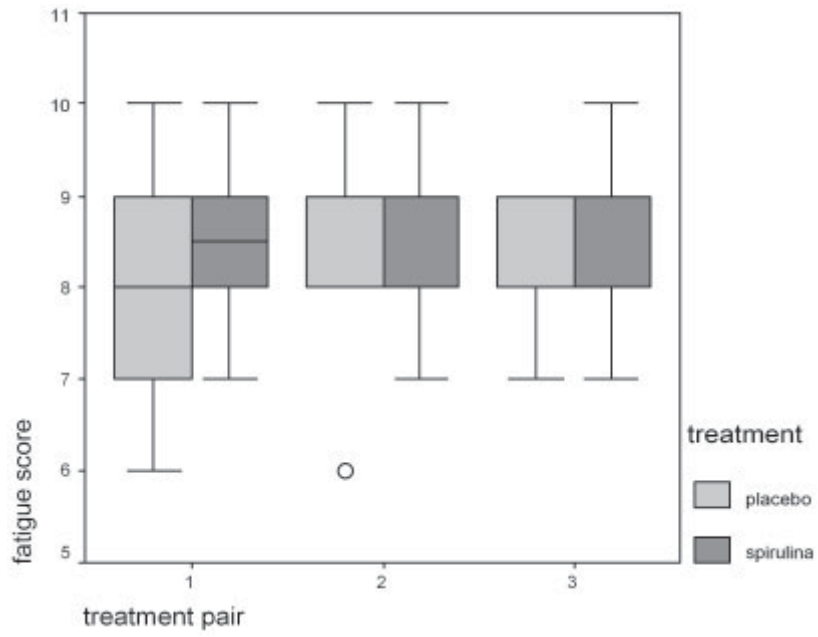


Figure 4. Fatigue scores evolution in patient 3.

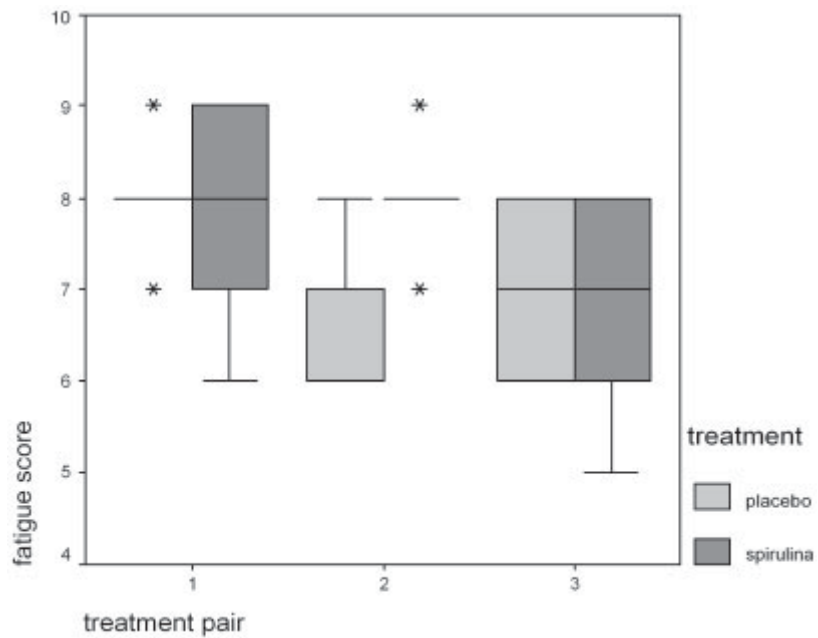


Figure 5. Fatigue scores evolution in patient 4.

Table 1. Results of the N-of-1 RCT of spirulina in four subjects with asthenia

Patient	Pair	Treatment	Mean fatigue score	p
1	1	Spirulina	6.21	0.7963
		Placebo	6.36	
		Difference	-0.15	
	2	Spirulina	6.21	
		Placebo	6.29	
		Difference	+0,08	
	3	Spirulina	6.29	
		Placebo	6.36	
		Difference	-0.07	
2	1	Spirulina	6.29	0.5426
		Placebo	6.36	
		Difference	-0.07	
	2	Spirulina	7.64	
		Placebo	7.43	
		Difference	+0.21	
	3	Spirulina	7.00	
		Placebo	7.70	
		Difference	-0.79	
3	1	Spirulina	8.43	0.1007
		Placebo	7.93	
		Difference	+0.50	
	2	Spirulina	8.57	
		Placebo	8.36	
		Difference	+0.21	
	3	Spirulina	8.71	
		Placebo	8.50	
		Difference	+0,21	
4	1	Spirulina	7.86	0.4560
		Placebo	8.00	
		Difference	-0.14	
	2	Spirulina	7.93	
		Placebo	6.57	
		Difference	+0.64	
	3	Spirulina	7.07	
		Placebo	7.00	
		Difference	+0.07	