Original Research Article

Phosphatidylserine Containing Omega-3 Fatty Acids May Improve Memory Abilities in Nondemented Elderly Individuals with Memory Complaints: Results from an Open-Label Extension Study

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Key Words

Phosphatidylserine · Omega-3 fatty acids · Docosahexaenoic acid · Cognitive decline · Memory complaints

Abstract

Background: The present study is an open-label extension (OLE) aimed at evaluating the effect of 100 mg/day of phosphatidylserine enriched with docosahexaenoic acid (PS-DHA) on cognitive performance in nondemented elderly individuals with memory complaints. **Methods:** From the participants who completed the core study, 122 continued with a 15-week OLE. Efficacy was assessed using a computerized tool and the Clinical Global Impression of Change (CGI-C) rating scale. **Results:** A significant improvement in sustained attention and memory recognition was observed in the PS-DHA naïve group, while the PS-DHA continuers maintained their cognitive status. Additionally, a significant improvement in CGI-C was observed in the naïve group. **Conclusions:** The results demonstrate that consumption of 100 mg/day of PS-DHA might be associated with improving or maintaining cognitive status in elderly subjects with memory complaints.

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Introduction

Phosphatidylserine (PS) is one of the major phospholipids in mammalian cell membranes and it plays important roles in dynamic membrane functions [1, 2]. With aging, neural membrane fluidity is compromised due to the increased presence of cholesterol, a low incor-

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poration rate and decreased levels of total polyunsaturated fatty acids, blockages to phospholipid pathways, and increases in free radicals, resulting in oxidative stress [3]. The brain is one of the richest organs in lipid content, and its structure and function have been shown to be influenced by nutrients [4]. Unfavorable changes in the brain phospholipid levels (lipid imbalance) could lead to different pathogenic processes [5], as demonstrated in various neuronal conditions. Clinical trials, conducted in the early 1990's, indicated that consumption of 100–300 mg/day of PS extracted from bovine cortex (BC-PS) plays important roles in the support of mental functions in the aging brain [6–8]. BC-PS was found to be enriched with docosahexaenoic acid (DHA) [9]. However, due to safety concerns of potential contamination by bovine spongiform encephalopathy prions, BC-PS is no longer available. Alternatives such as soybean-derived PS are considered a safe alternative; however, soybean-derived PS does not contain DHA, and clinical studies have demonstrated inconclusive efficacy results [10, 11]. We have recently reported on a safe sourced PS enriched with DHA (PS-DHA) to have beneficial effects in nondemented elderly individuals with memory complaints [12]. In this study, subjects with memory complaints were randomized to receive either PS-DHA or placebo for 15 weeks. Efficacy measures, assessed at baseline and endpoint, included the Rey Auditory Verbal Learning Test, Rey Complex Figure Test, and others. At the end of a 15-week, double-blinded, placebo-controlled study, verbal immediate recall was significantly improved in the PS-DHA group compared to the placebo group. Interestingly, post hoc analysis revealed that participants with a relatively good cognitive performance at baseline were most likely to benefit. The safety profile of PS-DHA following a 30-week administration was also reported [13]. Briefly, PS-DHA was found to be safe and well tolerated, with no significant side effects.

Here, we report the efficacy results of a 15-week, open-label extension (OLE) study that followed the double-blind, placebo-controlled phase previously described. In this extension, the participants consumed 100 mg/day of PS-DHA.

Methods

Study Design and Participants

Detailed methods of the 15-week, double-blind, placebo-controlled core study (clinicaltrials.gov identifier: NCT00437983) have been published previously [12]. Briefly, participants were recruited through advertisements in senior citizens homes, hospitals, and newspapers. A total of 157 nondemented individuals with memory complaints met the inclusion criteria and were assigned to the study groups according to a computerized randomization process, receiving 300 mg/day of PS-DHA or identical-looking placebo (cellulose). In total, 131 participants completed the double-blind, placebo-controlled phase. The completers were invited to continue with a 15-week OLE (without breaking patients' blinded treatment code), and 122 participants agreed to continue. During the OLE, all participants received 100 mg/day of PS-DHA, providing 100 mg of PS and an equivalent amount of 26 mg of DHA+EPA (eicosapentaenoic acid; DHA/EPA ratio 3:1). Participants who received 300 mg/day of PS-DHA during the double-blind phase and continued to receive 100 mg/day of PS-DHA during the OLE are hereafter referred to as continuers ($n = 61$), while participants who received placebo during the double-blind phase and switched to 100 mg/day of PS-DHA during the OLE are hereafter referred to as naïve ($n = 61$). PS-DHA (Vayacog®) was supplied by Enzymotec Ltd., Migdal HaEmeq, Israel. For treatment adherence monitoring, the participants returned all treatment packs at the study end point, and adherence was calculated from the number of the remaining capsules.

The study was conducted according to the principles of the Declaration of Helsinki and good clinical practice. The protocol was approved by the Ethics Committee of the Sourasky Medical Center, Tel Aviv, Israel, and all volunteers gave written informed consent prior to participation.

Assessments

Efficacy measurements included both objective reports and subjective measurements, assessed at the end of the double-blind phase (baseline of the OLE) and at the end of the OLE (after 15 weeks). As objective

Fig. 1. Study flowchart. A total of 122 subjects participated in the OLE, and 121 were included in the per-protocol efficacy analysis.

measurements, a computerized neuropsychological assessment tool, NexAde™, was used [14]. This software consists of seven separate tasks: symbol spotting, pattern identification, pattern recall, digit-symbol substitution, digits span forward, digits span backward, and delayed pattern recall. Based on the results obtained in the single tasks, cognitive composite scores are calculated for focused attention, sustained attention, memory recognition and recall, visuospatial learning, spatial short-term memory, and a final score, which summarizes all composite score results. All tasks are computer-controlled [14]. The Clinical Global Impression of Change (CGI-C) rating scale was used to obtain subjective perceptions of improvement. Using the participants' cognitive status impression at the beginning of the OLE as a reference, the evaluator interviewed the participants at the end of the OLE in order to obtain an impression of change during the OLE period. The global improvement score ranges from 1 = 'very much improved', through 4 = 'no change', to 7 = 'very much worse'. The interviewer had no access to the cognitive test scores and adverse event reports obtained as part of the protocol. To examine the differences between the treatment groups in the assessment of global change, participants who experienced an improvement (scores 1–3) on the last visit were classified as 'improved' over the treatment period. Otherwise, participants were classified as 'unchanged' (score 4) or as 'worse' (scores 5–7).

Safety evaluation included physical examination, blood pressure, heart rate, and weight. Adverse events were also monitored.

Statistical Analysis

Results are expressed as mean ± standard error (SE). Student's t test for independent samples was used to evaluate differences in demographic and baseline continuous variables. Pearson's χ^2 test was used for the analysis of categorical variables and CGI-C. Data analysis was performed according to participants' randomization to treatment or placebo in the preceding double-blind phase. Within-group analysis was tested for the naïve and continuers groups, using paired Student's t test analysis. All statistical tests were two-tailed, and significance was set at a level of 0.05. SAS statistical package (version 9.1) was used for all analyses.

Results

Participants

A flow diagram of the study participants throughout the OLE is presented in figure 1.

Of the 122 participants enrolled in the OLE, 61 were continuers and 61 were naïve. One participant from the PS-DHA naïve group was excluded from the study due to protocol violation. Baseline characteristics of the study participants who completed the OLE are

Table 1. Baseline characteristics of the study completers

Characteristic	PS-DHA naïve (n = 60)	PS-DHA continuers (n = 61)	p*
Age, years	72.4±8.3	72.1±7.9	0.800
Male gender	53.3	47.5	0.524
Married	73.3	65.6	0.354
Education, years	13.3±3.6	13.3±3.8	0.987
Academic education	45.0	49.2	0.645
Compliance**	93.2±8.8	95.4±6.2	0.120
MAC-Q	29.2±2.6	29.9±2.9	0.154
MMSE score	28.8±1.1	28.4±1.2	0.053
CDR = 0	91.7	83.6	0.179
GDS score	1.2±1.2	1.3±1.2	0.774
GDS >2	18.3	19.7	0.851

Values are mean ± SD or %. MAC-Q = Memory Complaints Questionnaire; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating Scale; GDS = Geriatric Depression Scale (short version).

* Based on the two-tailed Student's t test for continuous variables and Pearson's χ^2 test for categorical variables.

** Compliance data were obtained for 55 and 59 participants from the PS-DHA naïve and the PS-DHA continuers groups, respectively.

presented in table 1. No significant differences in demographic or cognitive status were observed between the two study groups. High treatment compliance during the open label phase (<90%) was observed in both groups.

Efficacy Assessment

Neurological Computerized Cognitive Assessment Tool

Following 15 weeks of open label treatment with PS-DHA, no significant change in cognitive abilities was observed in the continuers group (fig. 2a). A different pattern was observed in the naïve group, where the results showed an improvement in six out of seven tested parameters, reaching the statistically significant level ($p < 0.05$) in sustained attention, memory recognition, and in the cognitive assessment final score (fig. 2b).

Clinical Global Impression of Change

Within the continuers group, the number of participants who were judged as clinically improved at the end of the double-blind phase was 25 (38%), similar to the number of participants who were judged as clinically improved at end of the OLE (24, 40%). Sixteen participants out of the 25 clinically improved subjects at the end of the double-blind phase were also judged as clinically improved during the OLE, while 7 participants maintained their improvement and reported no further change during the OLE.

Within the naïve group, the number of participants who were judged as clinically improved at the end of the double-blind phase was 18 (28%). A significantly higher number of participants (26, 44%; $p = 0.019$) was judged as clinically improved at the end of the OLE. Fourteen participants out of the 18 clinically improved subjects at the end of the double blind phase were also judged as clinically improved during the OLE, while 2 participants maintained their improvement and reported no further change during the OLE.

Fig. 2. Cognitive performance during the OLE. Data were obtained from 54 participants from the PS-DHA continuers group (**a**) and from 55 participants from the PS-DHA naïve group (**b**) at the end of the double-blind, placebo-controlled phase (empty bars) and at the end of the OLE (filled bars). Data are presented as mean ± SE; * $p < 0.05$ based on a two-tailed paired Student's t test.

Safety

Adverse events and the safety report have been published previously [13]. Briefly, a reduction in resting diastolic blood pressure and a slight weight gain were observed among the continuers. While only three adverse events, classified by the study physicians as related

or probably related to the study treatment (gastrointestinal discomfort, headache and tenesmus), were reported in the continuers group, no related or probably related side effects were reported in the naïve group.

Discussion

This OLE study followed a 15-week, double-blind, placebo-controlled study of PS-DHA consumption at a dose of 300 mg/day. During the double-blind study, the PS-DHA group showed a significant improvement in memory (immediate recall) in nondemented subjects with memory complaints. Post hoc analysis suggested that participants with a relatively good cognitive performance at baseline responded better to the treatment [12]. During the 15-week OLE, consumption of 100 mg/day of PS-DHA was associated with a sustained cognitive status of participants previously treated with 300 mg/day of PS-DHA, while naïve participants attained a significant improvement in sustained attention and memory.

The tested marine-derived PS-DHA is considered safe [13], without any contamination concerns for PS derived from bovine brain. Consumption of 100 mg/day of PS-DHA was well tolerated, supported by the absence of any significant adverse events and by only a single exclusion during this extension phase.

The findings of this OLE study add to the accumulating data that support the positive effect of PS containing omega-3 fatty acids on cognitive performance. In previous studies, administration of 200–300 mg/day of PS containing omega-3 fatty acids was found to have beneficial effects, purely symptomatic or neuroprotective [9, 15–19] ones, on various types of cognitive impairment, ranging from age-associated cognitive decline to Alzheimer's disease [7, 8, 20–24].

In a double-blind, placebo-controlled study, administration of BC-PS to patients with age-associated memory impairment improved their performance related to learning and memory tasks of daily life [8]. Geriatric patients treated with BC-PS significantly improved in behavioral and cognitive parameters [6]. In cognitively impaired populations, the measurement of the regional cerebral metabolic rate for glucose in AD patients using positron emission tomography and ¹⁸F-2-fluoro-2-deoxy-D-glucose as well as electrophysiological changes with electroencephalography indicated that BC-PS treatment has an effect on brain function [18, 25]. These changes were further correlated with neuropsychological improvements [7, 21].

The results of this OLE show for the first time that 100 mg/day of PS-DHA might significantly improve cognitive abilities in nondemented elderly individuals with memory complaints (naïve) and may preserve the effect observed following administration of 300 mg/day of PS-DHA during the double-blinded phase (continuers). These results, together with previous findings reported for BC-PS, justify further studies evaluating the effect of PS-DHA also in more severely affected populations.

While the findings obtained throughout this OLE study are encouraging, we acknowledge certain limitations. One limitation of the current study is its open-label nature and the absence of a placebo-controlled group; therefore, there is a risk of bias in the interpretation of the study results. Nonetheless, the fact that a significant improvement was observed only in the naïve group (the subjects were not informed that they have previously been in the placebo arm) suggests that the effect is genuine and not derived from the placebo or learning effect. This was further supported by the fact that the significant improvement was observed in both the objective and the subjective measurements (computerized tool and CGI-C, respectively). To conclude, the current OLE suggests that consumption of 100 mg/day of PS-DHA might maintain or improve cognitive status in subjects with memory complaints. These preliminary results are encouraging and could assist in planning an extended, double-blind, placebo-controlled study to further establish the efficacy of this dose.

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