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Effects of Plasmalogen on Patients with Mild Cognitive Impairment: A Randomized, Placebo-Controlled Trial in Japan

Takehiko Fujino[1]*, Tatsuo Yamada[2], Takashi Asada[3], Midori Ichimaru[4], Yoshio Tsuboi[5], Chikako Wakana[6] and Shiro Mawatari[1]

[1]*Institute of Rheological Functions of Food, 2241-1 Kubara, Hisayama-machi, Kasuya-gun, Fukuoka 811-2501, Japan*
[2]*Gotanda Rehabilitation Hospital, 8-8-20 Nishigotanda, Shinagawa-ku, Tokyo 141-0031, Japan*
[3]*Memory Clinic Ochanomizu, 1-5-34, Yushima, Bunkyo-ku, Tokyo 113-0034, Japan*
[4]*BOOCS Holistic Clinic Tokyo, 3-4-1 Ginza, Chuo-ku, Tokyo 104-0061, Japan*
[5]*Department of Neurology, School of Medicine, Fukuoka University, 7-45-1 Nanakuma, Johnan-ku, Fukuoka 814-0180, Japan*
[6]*BOOCS Clinic Fukuoka, 6-18 Tenya-machi, Hakata-ku, Fukuoka 812-0025, Japan*

Abstract

Objective: It has been shown that plasmalogens (Pls) in the brain tissue and blood decrease among Alzheimer's disease (AD) patients. We first confirmed the effects of Pls on animal AD models, and subsequently reported that the ingestion of 1 mg Pls was effective for AD patients in a randomized, placebo-controlled trial with mild cognitive impairment (MCI) or mild AD patients. The present study examined the efficacy of orally administered Pls on patients with MCI enrolled in the previous trial in terms of individual domains of the Mini Mental State Examination-Japanese (MMSE-J).

Methods: The present analysis used 178 patients with MCI out of the 276 patients with either MCI or AD in the previously reported trial, and assessed the 24 week change in the domain-specific scores of the MMSE-J. Originally, the randomized, placebo-controlled trial was performed for 276 patients at age of 60-85 years who had the MMSE-J score of 20-27 points and the Geriatric Depression Scale-Short Version-Japanese Version (GDS-S-J) score of 5 points or less. The patients were randomly allocated to either a treatment with 1 mg of scallop-derived Pls daily or a placebo treatment. The primary outcome was a 24 week change in the MMSE-J. The registered number of the trial is UMIN000014945.

Results: The MMSE-J total score improved statistically significantly in the Pls treatment but not in the placebo treatment, resulting in no significant between-treatment difference. With respect to one of the MMSE-J domains, orientation to place, the Pls treatment showed a significant improvement and the placebo treatment showed no such improvement; the between-treatment difference was statistically significant (p=0.003). The *domain* for orientation to time worsened significantly at endpoint in the placebo treatment, while the Pls treatment showed no worsening. However, the between-treatment difference failed to reach the statistical significance. No significant change was found in either treatment regarding the other MMSE-J domains.

Conclusion: These findings suggest that oral administration of 1 mg Pls enhances cognitive function of MCI patients, especially orientation to place.

Keywords: Mild cognitive impairment; Alzheimer's disease; Plasmalogen; Mini mental state examination; Orientation to place

Introduction

The prevalence of Alzheimer's disease (AD) has markedly increased worldwide. Early diagnosis and treatment of the preclinical stage of AD are, therefore, an urgent task for not only patients but for people living with dementia and social costs [1]. In general, mild cognitive impairment (MCI) is a clinical transition phase between normal elderly and AD. Internationally, the prevalence of MCI is estimated to be 15% to 20% in those at the age of 60 years and older [2]. It is also estimated that the progression from MCI to dementia occurs at annual rates of 8% to 15% [2]. Therefore, MCI is an important condition to identify and treat as early as possible. The interventions, especially pharmacological randomized control trials, have been attempted to delay MCI from the progress into AD. None of those, however, has been successful in delaying the progression from MCI to AD dementia [3-5]. Recently, it has become clear that plasmalogens (Pls), a special class of glycerophospholipids, are closely related to AD and MCI. Pls were decreased in the postmortem brain of AD patients [6-8] and Pls levels in the plasma and erythrocytes were lowered among AD and MCI patients [9-10].

Moreover, we have developed the simple method to extract Pls from animals [11] and subsequently have enabled to study preventive and therapeutic effects of Pls on animal AD model [12-15]. Interestingly, one of these experiments revealed that Pls resulted in a prominent improvement of space memory [16], which may be equivalent to human place-orientation. We have also reported that Pls may improve the cognitive function of mild AD patients in a randomized controlled trial (RCT) in which scallop-derived Pls were orally administered for 24 weeks [17]. In that study, a cognitive function was evaluated by the Mini Mental State Examination-Japanese (MMSE-J), but we did not examine the domain-specific changes of the MMSE-J. The present study examined the changes in the scores of individual domains of MMSE-J to assess the effects of scallop-derived plasmalogen on MCI patients in the previously reported RCT.

***Corresponding author:** Takehiko Fujino, Institute of Rheological Functions of Food, 2241-1 Kubara, Hisayama-machi, Kasuya-gun, Fukuoka 811-2501, Japan, Tel: +81 92 273 2420; E-mail: fujino-t@boocsclinic.com

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Methods

The study subjects in the present analysis were 178 patients with MCI out of the 276 patients with either MCI or AD who had completed the previously reported 24 week RCT [17]. Details of the methods have been described in the previous report [17]. In brief, the study was a multicenter, randomized, placebo-controlled trial of 276 patients at the age of 60 to 85 years who had a score of 20 to 27 points in the MMSE-J [18] and a score of 5 or less points in the Geriatric Depression Scale-Short Version-Japanese (GDS-S-J) [19]. The diagnosis of MCI was based on the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), and the MCI patients had 24 to 27 points of the MMSE-J [20]. The eligible patients were randomly allocated to either a treatment with 1 mg of Pls purified from scallop daily or a placebo treatment. The total score of MMSE-J was an outcome of the primary interest. All of the patients or their caretakers gave written informed consent. The trial was approved by the Institutional Review Boards of Fukuoka University Hospital (Fukuoka), Nihonbashi Sakura Clinic (Tokyo) and BOOCS Clinic Fukuoka (Fukuoka), was conducted in compliance with the Declaration of Helsinki.

The MMSE-J score was calculated on the basis of the response to 11-item questions at weeks 0, 12, 24 and 28. At each visit, the patient was accompanied by his/her caretaker. In the present analysis, the measurements at baseline and 24 weeks were used, and scores of the 11 domains were compared between the two treatments. Individual items of the MMSE-J are explained in Appendix 1.

The changes in the total score and domain-specific scores of the MMSE-J at endpoint were compared between the two using unpaired t-test. The after-treatment change from the baseline was statistically evaluated using paired t-test, and the mean change and 95% confidence interval (CI) were presented. Statistical analyses were carried out using Stata version 13 (StataCorp, College Station, TX). The registered number of the trial is UMIN000014945.

Results

The number of MCI patients in the Pls and placebo treatments was 90 and 88, respectively. No measurable difference was noted at baseline between the two treatments regarding sex, age, years of education, MMSE-J total score and domain-specific scores (Table 1).

The MMSE-J total score increased at 24 weeks by 0.59 (95% CI 0.13:1.05, p=0.01) in the Pls treatment and by 0.39 (95% CI -0.18:0.95, p=0.18) in the placebo treatment. However, the between-treatment difference in the change of the MMSE-J *total score* was not statistically significant (Figure 1).

Of the 11 domains of the MMSE-J, the orientation to place improved statistically significantly in the Pls treatment (p<0.0001), but not in the placebo treatment (p=0.66). The change in the *domain score was* significant*ly* different between the two treatments (p=0.003) (Figure 1 and Table 2).

As regards the orientation to time, the Pls treatment showed no appreciable baseline-to-endpoint change (p=0.94) while the placebo treatment showed a statistically significant deterioration at endpoint compared to baseline (p=0.03). However, the between-treatment difference in the change of the score for the orientation to time was not statistically significant (Figure 1 and Table 2). Regarding the domains of calculation, registration and other domains, there was no significant change in either treatment. Nor was there a significant between-treatment difference at endpoint (Table 2).

Variable	Plasmalogen (n=90)	Placebo (n=88)	P value*
Male, n (%)	37 (41.1)	26 (29.5)	0.12
Age in year	75.8 (6.1)	75.9 (5.5)	0.90
Years of education†	12.7 (2.9)	12.1 (2.1)	0.11
MMSE-J	25.6 (1.3)	25.6 (1.1)	0.99
1. Orientation to time	4.1 (1.2)	4.1 (1.0)	0.75
2. Orientation to place	4.3 (0.6)	4.4 (0.6)	0.13
3. Three-word registration	3.0 (0.2)	3.0 (0.3)	0.98
4. Attention and calculation	4.2 (1.0)	3.9 (1.2)	0.07
5. Three-word recall	1.4 (1.0)	1.5 (1.1)	0.55
6. Language (naming)	2.0 (0.2)	2.0 (0.2)	0.99
7. Language (repeating)	1.0 (0.1)	1.0 (0.2)	0.55
8. Language (3-step command)	2.8 (0.5)	2.8 (0.4)	0.66
9. Language (reading)	1.0 (0.0)	1.0 (0.0)	—
10. Language (writing)	1.0 (0.2)	1.0 (0.2)	0.98
11. Visual construction	1.0 (0.2)	1.0 (0.2)	0.72

MMSE-J: Mini Mental State Examination-Japanese
Values are mean (SD) unless otherwise specified
* Chi-square test for proportion and unpaired t-test for mean
† Number of the patients was 86 in the plasmalogen treatment and 85 in the placebo treatment

Table 1: Baseline characteristics.

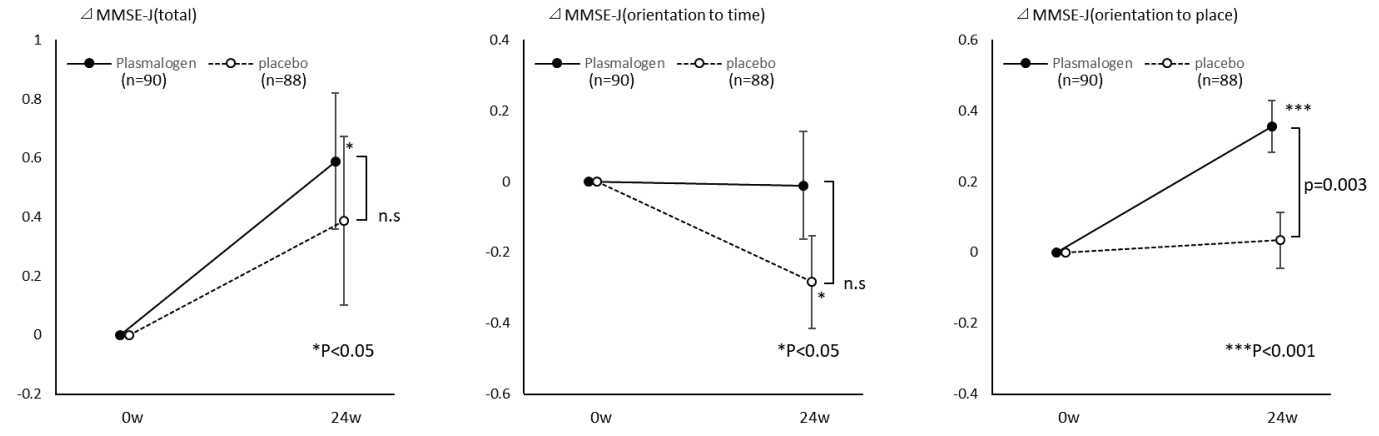

Figure 1: Change in MMSE-J score after Pls administration (MCI).

MMSE-J domain	Plasmalogen (n=90)			Placebo (n=88)			P-value
	Mean	SD	(95% CI)	Mean	SD	(95% CI)	
1. Orientation to time	-0.01	1.45	(-0.31: 0.29)	-0.28	1.23	(-0.54: -0.02)	0.18
2. Orientation to place	0.36	0.69	(0.21: 0.50)	0.03	0.73	(-0.12: 0.19)	0.003
3. Three-word registration	0.02	0.26	(-0.03: 0.08)	0.05	0.26	(-0.01: 0.10)	0.55
4. Attention and calculation	0.10	1.20	(-0.15: 0.35)	0.24	1.42	(-0.06: 0.54)	0.48
5. Three-word recall	0.00	1.07	(-0.22: 0.22)	0.24	1.22	(-0.02: 0.50)	0.17
6. Language (naming)	0.02	0.21	(-0.02: 0.07)	0.02	0.15	(-0.01: 0.05)	0.99
7. Language (repeating)	0.01	0.11	(-0.01: 0.03)	0.02	0.15	(-0.01: 0.05)	0.55
8. Language (3-step command)	0.06	0.57	(-0.06: 0.17)	0.07	0.52	(-0.04: 0.18)	0.88
9. Language (reading)	0.00	0.00	(—)	0.00	0.00	(—)	—
10. Language (writing)	0.03	0.18	(0.00: 0.07)	0.02	0.21	(-0.02: 0.07)	0.72
11. Visual construction	0.00	0.21	(-0.04: 0.04)	-0.02	0.26	(-0.08: 0.03)	0.52

MMSE-J: Mini Mental State Examination-Japanese

Table 2: Mean difference from baseline by MMSE-J domains.

MMSE-J domain	Plasmalogen			Placebo			P-value
	Mean	SD	(95% CI)	Mean	SD	(95% CI)	
Aged ≤ 77 years	**(n=48)**			**(n=52)**			
1. Orientation to time	-0.10	1.31	(-0.48: 0.28)	-0.40	1.30	(-0.77: -0.04)	0.25
2. Orientation to place	0.44	0.71	(0.23: 0.64)	0.00	0.71	(-0.20: 0.20)	0.003
3. Three-word registration	0.02	0.25	(-0.05: 0.09)	0.04	0.28	(-0.04: 0.12)	0.74
4. Attention and calculation	0.10	1.17	(-0.24: 0.44)	0.44	1.42	(0.05: 0.84)	0.20
5. Three-word recall	0.25	1.06	(-0.06: 0.56)	0.31	1.13	(-0.01: 0.62)	0.79
6. Language (naming)	0.04	0.29	(-0.04: 0.13)	0.04	0.19	(-0.02: 0.09)	0.95
7. Language (repeating)	0.02	0.14	(-0.02: 0.06)	0.04	0.19	(-0.02: 0.09)	0.61
8. Language (3-step command)	0.15	0.55	(-0.01: 0.30)	0.06	0.50	(-0.08: 0.20)	0.40
9. Language (reading)	0.00	0.00	(—)	0.00	0.00	(—)	-
10. Language (writing)	0.06	0.24	(-0.01: 0.13)	0.04	0.19	(-0.02: 0.09)	0.59
11. Visual construction	0.02	0.25	(-0.05: 0.09)	-0.02	0.31	(-0.11: 0.07)	0.48
Aged ≥78 years	**(n=42)**			**(n=36)**			
1. Orientation to time	0.10	1.61	(-0.40: 0.60)	-0.11	1.12	(-0.49: 0.27)	0.52
2. Orientation to place	0.26	0.66	(0.05: 0.47)	0.08	0.77	(-0.18: 0.34)	0.28
3. Three-word registration	0.02	0.27	(-0.06: 0.11)	0.06	0.23	(-0.02: 0.13)	0.58
4. Attention and calculation	0.10	1.25	(-0.29: 0.48)	-0.06	1.39	(-0.53: 0.42)	0.62
5. Three-word recall	-0.29	1.02	(-0.60: 0.03)	0.14	1.36	(-0.32: 0.60)	0.12
6. Language (naming)	0.00	0.00	(—)	0.00	0.00	(—)	—
7. Language (repeating)	0.00	0.00	(—)	0.00	0.00	(—)	—
8. Language (3-step command)	-0.05	0.58	(-0.23: 0.13)	0.08	0.55	(-0.10: 0.27)	0.31
9. Language (reading)	0.00	0.00	(—)	0.00	0.00	(—)	—
10. Language (writing)	0.00	0.00	(—)	0.00	0.24	(-0.08: 0.08)	1.00
11. Visual construction	-0.02	0.15	(-0.07: 0.02)	-0.03	0.17	(-0.08: 0.03)	0.91

MMSE-J: Mini Mental State Examination-Japanese

Table 3: Mean difference from the baseline in the domains of MMSE-J by age group.

Further analyses were performed with stratification by age group and gender. The age was categorized into two classes at the median age in the original RCT of 276 patients, namely less than 77 years and 78 years or older. The differential improvement of the orientation-to-place score in the Pls treatment was observed in the patients aged 77 year or younger, but not in those aged 78 year or older (Table 3). Although the between-treatment difference was less marked, the favorable change of the orientation-to-place score in the Pls treatment was observed in both men and women (Table 4).

The domain-specific analysis was repeated in the patients with mild AD (n=98). There was no measurable within-treatment change in either treatment and no material between-treatment difference in the change regarding any of the 11 domains of MMSE-J (Appendix 2).

Discussion

Our previous paper suggested that ingestion of Pls was effective in improving the cognitive function as captured by WMS-R among patients with mild AD [17]. Its effectiveness against MCI was, however, not observed; WMS-R improved in both Pls and placebo treatments, resulting in no significant between-treatment difference.

The present study examined the change in MMSE-J before and after Pls administration, focusing on MCI patients out of the patients enrolled in the previous RCT [17]. While the MMSE-J total score improved statistically significantly in the Pls treatment, the change was not significantly different from that observed in the placebo treatment. However, the analysis on individual domains of the MMSE-J revealed

MMSE-J domain	Plasmalogen			Placebo			P-value
	Mean	SD	(95% CI)	Mean	SD	(95% CI)	
Males	**(n=37)**			**(n=26)**			
1. Orientation to time	0.24	1.62	(-0.30: 0.78)	-0.50	1.61	(-1.15: 0.15)	0.08
2. Orientation to place	0.30	0.66	(0.08: 0.52)	-0.12	0.77	(-0.42: 0.19)	0.03
3. Three-word registration	-0.03	0.29	(-0.12: 0.07)	0.00	0.00	(—)	0.63
4. Attention and calculation	0.16	1.42	(-0.31: 0.64)	0.38	1.60	(-0.26: 1.03)	0.56
5. Three-word recall	-0.16	0.99	(-0.49: 0.17)	0.12	1.21	(-0.37: 0.60)	0.32
6. Language (naming)	0.05	0.33	(-0.06: 0.16)	0.00	0.00	(—)	0.41
7. Language (repeating)	0.00	0.00	(—)	0.04	0.20	(-0.04: 0.12)	0.24
8. Language (3-step command)	0.05	0.52	(-0.12: 0.23)	-0.04	0.53	(-0.25: 0.17)	0.49
9. Language (reading)	0.00	0.00	(—)	0.00	0.00	(—)	—
10. Language (writing)	0.05	0.23	(-0.02: 0.13)	0.08	0.27	(-0.03: 0.19)	0.72
11. Visual construction	-0.03	0.16	(-0.08: 0.03)	-0.04	0.34	(-0.18: 0.10)	0.86
Females	**(n=53)**			**(n=62)**			
1. Orientation to time	-0.19	1.30	(-0.55: 0.17)	-0.19	1.04	(-0.46: 0.07)	0.98
2. Orientation to place	0.40	0.72	(0.20: 0.59)	0.10	0.72	(-0.09: 0.28)	0.03
3. Three-word registration	0.06	0.23	(-0.01: 0.12)	0.06	0.31	(-0.01: 0.14)	0.88
4. Attention and calculation	0.06	1.03	(-0.23: 0.34)	0.18	1.35	(-0.17: 0.52)	0.60
5. Three-word recall	0.11	1.12	(-0.20: 0.42)	0.29	1.23	(-0.02: 0.60)	0.43
6. Language (naming)	0.00	0.00	(—)	0.03	0.18	(-0.01: 0.08)	0.19
7. Language (repeating)	0.02	0.14	(-0.02: 0.06)	0.02	0.13	(-0.02: 0.05)	0.91
8. Language (3-step command)	0.06	0.60	(-0.11: 0.22)	0.11	0.52	(-0.02: 0.24)	0.59
9. Language (reading)	0.00	0.00	(—)	0.00	0.00	(—)	—
10. Language (writing)	0.02	0.14	(-0.02: 0.06)	0.00	0.18	(-0.05: 0.05)	0.54
11. Visual construction	0.02	0.24	(-0.05: 0.08)	-0.02	0.22	(-0.07: 0.04)	0.42

MMSE-J: Mini Mental State Examination-Japanese

Table 4: Mean difference from the baseline in the domains of MMSE-J by gender.

that the orientation to place improved significantly and differentially in the Pls treatment alone. The lack of such an improvement among the patients 78 year or older suggests that the effects of Pls on MCI may be age-dependent. Lack of an improvement in the orientation to time by Pls is contrasting to the finding on place-orientation. The finding is, however, not necessarily peculiar in view of the temporal occurrence of disorientation to time and place. Orientation to time is usually disturbed at first, and then orientation to place is lost in the progression form MCI to AD [21,22]. Thus it is not a far-fetched explanation that recovery of the late-disturbed orientation to place precedes that of orientation to time. Importantly, the finding on the orientation to time suggests that Pls may prevent deterioration in orientation to time. Elsewhere, it has been demonstrated that Pls improve the spatial memory using the Morris Water Maze task [16], which is analogous to the place-orientation of the MMSE-J cognitive domains. Pls supplementation restored hippocampal levels of Pls and enhanced memory-related molecular signaling in model mice [16]. Therefore, these results strongly indicate that Pls improve the spatial memory in MCI patients as with animal AD models. Moreover, these findings are thought to have clinical importance since previous studies reported that the orientation to place of MMSE was an important predictor for elderly fall [23].

As discussed in our previous paper, ingestion of as small an amount of Pls as 1.0 mg per day has efficacy probably owing to its hormone-like action [24-26]. Pls are normally produced in peroxisomes and the ER in cells. However, its production capacity declines along with the occurrence and worsening of neuroinflammation, whereas Pls consumption increases. As a result, the total amount of Pls is decreased, which is thought to lead to the increase of γ-secretase [27] and accumulation of amyloid-β. It has become known that Pls are abundant in lipid rafts of cell membrane and improve cognitive function via the complicated process in cells [28].

Limitation

A limitation in this study is that the administration period of 24 weeks may be too short to fully evaluate MCI patients. Another weakness is that the cognitive function was assessed by the MMSE-J, which may be influenced by learning effect. However, such an effect was not observed in the placebo treatment regarding the orientation to place. Thus the present findings cannot be explained by learning effect alone. It should be also noted that the present finding on the orientation to place may have been due to chance. A statistically significant difference may occur by chance in the multiple comparisons. However, the between-treatment difference in the orientation to place was statistically significant (p=0.03) even after Bonferroni adjustment was made for the multiple comparisons. Further research is needed to conduct a follow-up study on change in MMSE-J along with measurement of blood Pls and MRI.

Conclusion

The present analysis assessed the 24 week change in the domain-specific scores of the MMSE-J among 178 patients with MCI enrolled in the previously reported trial. With respect to the orientation to place, the Pls treatment showed a significant improvement and the placebo treatment showed no such improvement. The between-treatment difference was highly significant (p=0.003). Oral administration of 1 mg Pls enhances cognitive function of MCI patients, especially the orientation to place.

Conflicts of Interest

TF and SM have applied for patents on method for manufacturing ether phospholipid (patent application number: PCT/JP2015/63617, PCT/JP2015/63740). TY, TA, MI, YT, and CW declare that they have no conflicts of interest.

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