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Among the various functions of Pls, special attention is focused on the antioxidant and anti-neuroin ammatory properties that are linked to the chemical structure of Pls characterized by the vinyl ether bond at the sn-1 position of glycerol backbone. Other well-known properties include ion transport, membrane fusion, cholesterol e ux, and precursor of biologically active substances. ese properties are all vital to maintain life [4-7].

We developed a simple method to extract large amounts of Pls from animals, and have accelerated research on Pls treatment and AD [16]. Our studies in animal models demonstrated that Pls reduced β-amyloid accumulation and improved cognitive and memory functions by suppressing neuroin ammation [17-19]. We further conducted a placebo-controlled trial, in which Pls were orally administered to

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Variable	All	Dose per day		*P* value*
		1.0 mg	0.5 mg	
Number of patients	*n* = 142	*n* = 74	*n* = 68	
Male, n (%)	54 (38.0)	32 (43.2%)	22 (32.4%)	0.18
Age in year	77.6 (5.2)	76.6 (4.9)	78.5 (5.3)	0.03
MMSE	13.2 (5.1)	13.4 (5.0)	13.0 (5.2)	0.66
Erythrocyte PlsPE (%)	7.88 (0.89)	7.90 (0.96)	7.86 (0.80)	0.78
Plasma PlsPE (mg/dl)†	2.96 (1.23)	3.10 (1.20)	2.83 (1.25)	0.22

Values are mean (SD) unless otherwise specifed.
MMSE= Mini-Mental State Examination.
PlsPE= phosphatidylethanolamine plasmalogen.
*Unpaired *t*-test for mean and chi-square test for proportions in the between-dose comparison.
†Number of patients: *n*=62 in the 1.0 mg group and *n*=63 in the 0.5 mg group.

Table 1: Baseline characteristics of participants.

CI = confdence interval.
MMSE= Mini-Mental State Examination.
PlsPE= phosphatidylethanolamine plasmalogen.
*Unpaired t-test for difference between 1.0 mg and 0.5 mg groups.
†Number of patients: *n*= 67 in the 0.5 mg group.
‡Number of patients: *n*= 62 in the 1.0 mg group and *n*= 63 in the 0.5 mg group.

Table 2: Mean changes at 12 weeks from baseline in MMSE score and blood plasmalogen levels by treatment.

signi cantly increased in the 1.0 mg group ($P<10^{-4}$) and 0.5 mg group ($P<10^{-6}$). e increase seemed to be greater in the 0.5 mg group, but the between-group di erence was far from the statistical signi cance (P=0.12). e item-speci c analysis showed a signi cant improvement with respect to orientation to time, orientation to place, three-word registration, attention and calculation, and three-word recall in the whole subjects. None of these changes did not signi cantly di er by treatment dose.

Both erythrocyte and plasma levels of PlsPE increased signi cantly in the whole patients (P=0.001 for erythrocyte PlsPE and $P<10^{-8}$ for plasma PlsPE). While the increase in erythrocyte PlsPE did not signi cantly di er in the 1.0 mg and 0.5 mg groups, plasma PlsPE increased more markedly in the 0.5 mg group than in the 1.0 mg group (P=0.001).

Ca ego ical a e men of po - ea men change in MMSE

e post-treatment MMSE score improved in more than half of the patients. Numbers of the patients according to improvement categories were: remarkable improvement 36 (25.4%), improvement 38 (26.8%), no change 52 (36.6%), and worsening 16 (11.3%). e distribution of improvement categories did not di er by dose group (P=0.65), as illustrated in Figure 2.

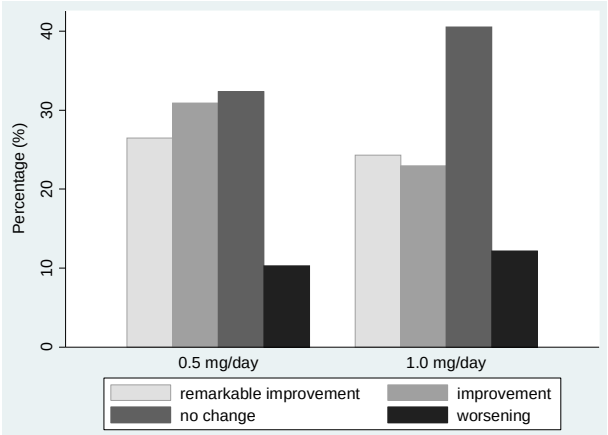

Figure 2: Categorical distribution of MMSE improvement by treatment dose in moderate-to-severe Alzheimer's disease. *P*= 0.65 for the between-group difference.

Rela ion of change in blood Pl PE o change in MMSE

e change in erythrocyte PlsPE, but not the change in plasma

PlsPE, showed a modest degree of correlation with the change in MMSE score (Figure 3). Pearson's correlation coe cients were 0.20 (P=0.01) for erythrocyte PlsPE and 0.12 (P=0.18) for plasma PlsPE.

Clinical afe,

Observed adverse events are listed in Table 3. Out of 157 participants enrolled in the study, 22 patients reported 23 adverse events. e reported adverse events were unrelated to the Pls treatment except for one episode, in which manic state was reported to be possibly related to Pls ingestion.

Di c ion and Concl ion

e present study showed that Pls ingestion resulted in an evident improvement in cognitive function as measured by MMSE in moderate-to-severe AD patients regardless of ingested dose (1.0 mg or 0.5 mg per day). e ndings add to evidence that Pls are bene cial in AD patients [20,21].

e present study did not set a control (placebo) group, thereby causing a concern that the observed bene cial e ect may have been ascribed to a placebo e ect. It is, however, conjectured that placebo e ect is unlikely to appear in moderate-to-severe AD in the same way as observed in general physical illnesses and symptoms. Patients with moderate-to-severe AD are considered to be less likely to develop the concepts of *e , ec a .* and *. , e* due to impaired cognitive function under the premise that placebo e ect is produced by patients' *e , ec a .* and *. , e* [23,24].

To address the magnitude of placebo e ect, we retrieved randomized-controlled trials of Japanese patients with moderate and severe AD by using PubMed and CiNii database. Studies of Japanese patients only were selected so as to eliminate ethnicity-related bias [25-27]. e placebo group in each study consistently exhibited a deterioration in cognitive function as measured by the Severe Impairment Battery and Alzheimer's Disease Assessment Scale-cognitive subscale in the 12-week period of treatment [25-27]. One of these studies measured MMSE and reported a decrease of 0.3 points at 24 weeks of placebo treatment [26]. While there is no direct evidence that placebo does not improve MMSE score at 12 weeks of treatment, placebo e ect, if any,

is unlikely to convert the natural course of deterioration in the MMSE score in AD patients [28,29]. It is notable that a quarter of the patients exhibited a remarkable improvement in cognitive function (increase of ≥ 4 points in MMSE). Furthermore, the positive correlation between the post-treatment change in erythrocyte PlsPE and the change in MMSE was an important nding to support the e ect of Pls improving cognitive function.

A clear improvement in MMSE was observed in both of the 1.0 mg and 0.5 mg groups, and no measurable di erence was observed between the two groups. It is very interesting that very small amounts of Pls had a favorable e ect on cognitive function. Recent studies have identi ed the counterpart of Pls among orphan G protein-coupled receptors on neuronal membrane, suggesting that Pls are a hormone-like substance [19,30,31]. is functional property may be a possible reason for Pls of small amounts such as 1.0 mg or 0.5 mg per day exerting an overt e ect of improving cognitive function.

It is also interesting that improvement was more remarkable in moderate-to-severe AD than in mild AD and MCI with the same dosage of Pls. In a previously reported study, patients with mild AD and MCI showed a small increase of 0.40 points in the MMSE score (95% CI 0.04–0.80 points) a er a 12-week of treatment with Pls of 1.0 mg/day [20]. It could be possible that patients with moderate-to-severe AD have relatively less normal brain tissue and more damaged tissue due to brain atrophy than those with mild AD and MCI, and therefore the former may demand and consume less hormone-like substance, Pls, than the latter. In addition, the latter is almost as high in the brain activity as healthy individuals, and thus consumes Pls as much as healthy individuals. On the other hand, the brain activity of moderate-to-severe AD is lower and consumes less Pls than that of healthy individuals. is hypothetical reasoning leads to a conclusion that even a very small amount of Pls is e ective for moderate-to-severe AD. Conversely, if a larger amount of Pls (i.e., 2–3 mg per day) is administered to mild AD and MCI, the same e ect as moderate-to-severe AD might be attained. Further studies concerning the dose-response e ect are needed to determine the in uence of severity.

Post-treatment Pls levels increased by 0.22% in erythrocytes and 0.70 mg/dL in plasma. It may be of interest how low the Pls levels at baseline were in comparison with the levels of normal subjects and to what extent the post-treatment Pls approached to the normal levels. In our unpublished data of 39 elderly aged 65-86 years with normal cognitive function (MMSE 29-30), the mean values of erythrocyte and plasma Pls were 8.56% (SD 0.94%) and 4.27 mg/dL (SD 1.07 mg/dL), respectively. At baseline, erythrocyte Pls were relatively 8% lower ($P<10^{-4}$) and plasma Pls were 31% lower ($P<10^{-7}$) as compared with the respective values of the normal elderly. e post-treatment erythrocyte and plasma Pls still remained to be 5% lower ($P=0.006$) and 14% lower ($P=0.03$), respectively. ese ndings suggest that the measurement of blood Pls is valuable to assess the severity and treatment progress in AD. It remains to be con rmed whether higher dosages of Pls can result in further increases in blood Pls levels nearer to the normal levels.

Plasma PlsPE increased more markedly a er treatment in the 0.5 mg group than in the 1.0 mg group while erythrocyte PlsPE did not show such a between-dose di erence. We have no clear explanation for this rather puzzling nding. e nding might be a chance because plasma PlsPE at baseline were slightly lower in the 0.5 mg group. Alternatively, there might be an unknown reason related to the interplay between erythrocyte and plasma Pls. Erythrocyte and plasma Pls were correlated with each other to some extent: Pearson's correlation coe cients were 0.33 for baseline values and 0.31 for post-treatment change. Further research is needed to clarify the e ects of Pls dose on erythrocyte and plasma levels of Pls.

is study has some problems and limitations including a short duration of Pls administration in addition to being open-labelled study. A randomized controlled trial of a longer period in patients with moderate-to-severe AD is highly warranted in the near future.

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