
Clinical Efficacy of Kippogen, which has Natural Herbs as its
Main Ingredient, on Dementia Patients

Data Analysis/Preparation and Explanation of Statistics

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Natural Medicine), under jurisdiction of the Ministry of Health, Labour, and
Welfare

Efficacy of Kippogen on Dementia Patients

Purpose

A compound drug (Kippogen) which natural herbs are its main ingredient, was given to patients with dementia, and clinical efficacy and safety were considered.

Subjects and Method

1. Subjects

Subjects comprised of 33 male and female cases, ages 71-100 years, who were randomly abstracted from outpatients and at-home patients of the clinic affiliated to Tennenbutsu Igaku Kenkyu Zaidan (Foundation of Research Institute of Natural Medicine), under jurisdiction of the Ministry of Health, Labour, and Welfare, and medical agencies under clinical contract. Of these, 5 cases were given a placebo.

2. Method

The test product (shown in Table 1) was administered to the subjects for 8 weeks between December 2003 and April 2004. Observation items regarding clinical symptoms, side effects and satisfaction of the subjects were measured from the day the study began, 4 weeks later, and 8 weeks later. Efficacy and safety of the test product were considered. Administration method was one packet (3.75 g) of the test product, administered twice a day. At the start of this study, details of the study, predicted efficacy, side-effects, etc., were explained to the patients, and consent to participate in the study was obtained.

Table 1

Test product

Kippogen (registered trademark)

1) Survey items

A. Mini-Mental State Examination (MMSE)

Significant difference was considered using Wilcoxon signed-rank test on the subjects, including those given a placebo.

B. Problem Behavior

Significant difference was considered using Wilcoxon signed-rank test on the subjects, including those given a placebo.

C. Side effects

Adverse events during the study were investigated and handled as side effects, excluding cases where causal relationship of the symptoms and the drug could be definitely denied.

D. Blood test (IGF-I, DHEA-S)

Significant difference in blood tests was considered using Wilcoxon signed-rank test.

E. Satisfaction Level

Significant difference in satisfaction of the subjects was considered using Wilcoxon signed-rank test.

Results

1. Subjects

Among 33 cases of patients participating in this study, 26 cases completed the 8 weeks of study period, and 7 cases discontinued it midterm. Subject Characteristics are shown in Table 2.

Table 2		Subject Characteristics	
	No. of Cases	Ave. Age	male/female
Cases at completion	26	85	9 / 17
Discontinued cases	7		1 / 6

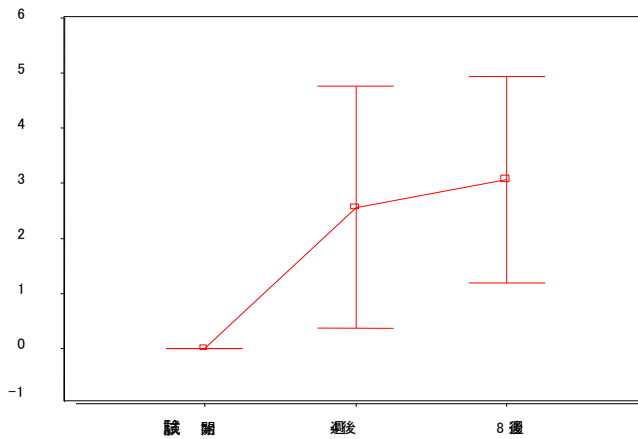
2. Effect on clinical symptoms

Changes in clinical symptoms (Observation item A-D), from the day the study was started and at 8 weeks later, are shown in the figure.

A. Change according to Mini-Mental State Examination (MMSE)

1. Change in study subjects and placebo subjects (control)

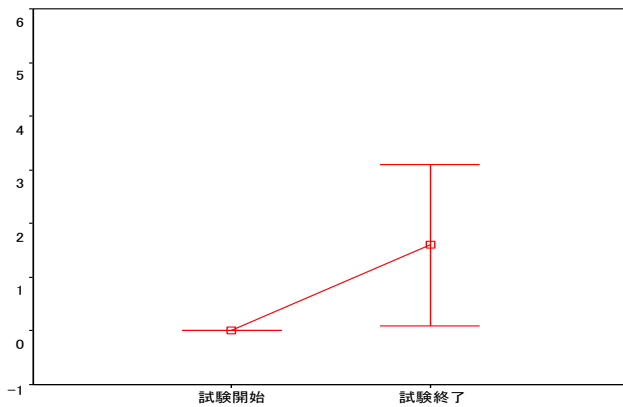
(1) Study subjects



When changes in all subjects of this study were surveyed using Wilcoxon signed-rank test, significant difference ($p < 0.005$) was observed at 8 weeks compared to the start of the study.

Figure 1. Change in MMSE over time

(2) Placebo subjects

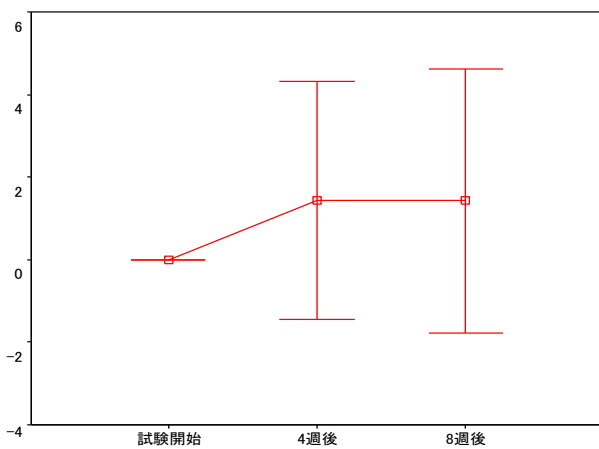


When changes in all placebo subjects were surveyed using Wilcoxon signed-rank test, no statistical significant difference ($p>0.05$) was observed.

Figure 2. Change in MMSE over time (placebo)

2. Difference in Effect by Age

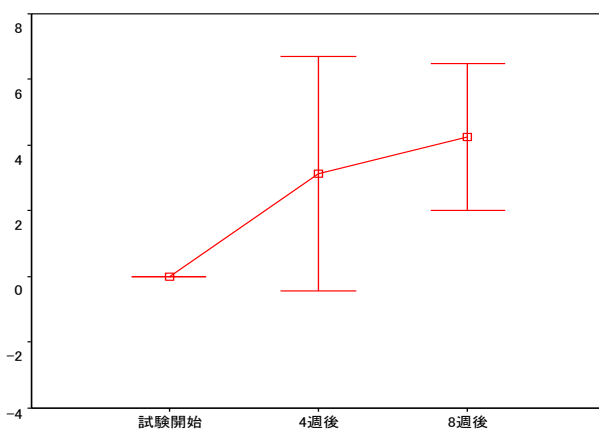
(1) MMSE of advanced elderly (75-84 years)



No statistical significant difference ($P>0.05$) was observed for the advanced elderly group (75-84 years old).

Figure 3. Change in MMSE in advanced elderly group over time

(2) MMSE of super advanced elderly group (85 years and older)



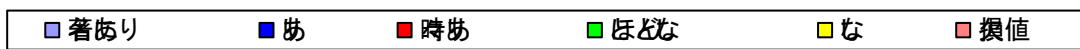
A statistical significant difference ($P<0.05$) was observed for the super advanced elderly group (85 years and older)

Figure 4. Change in MMSE in the super advanced elderly group over time

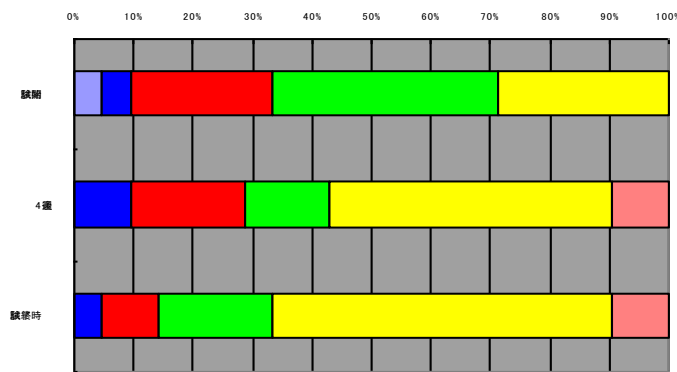
*There were fewer people in the elderly group (65-74 years) and placebo subjects, and this was not included in the statistics.

B. Change in Problem Behavior

Symptoms and behavior were surveyed and considered using daily life self-support degree criteria.

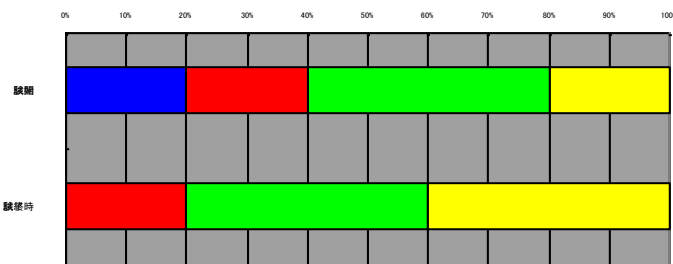


Frequently observed Observed Sometimes observed Hardly observed Not observed Lost value



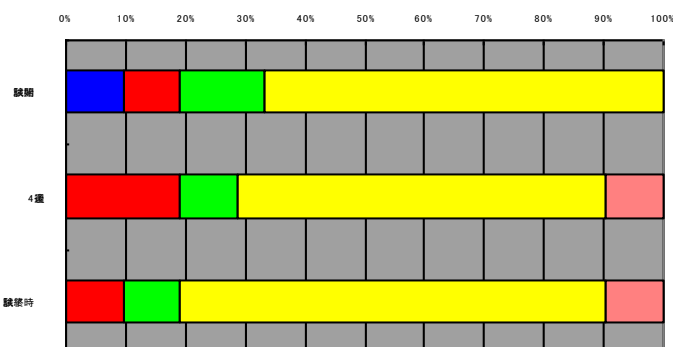
When change in day/night reversal was surveyed using Wilcoxon signed-rank test, a significant difference ($p < 0.05$) was observed at 4 weeks and at the completion of the study compared to the start of the study.

Figure 5. Change in day/night reversal over time



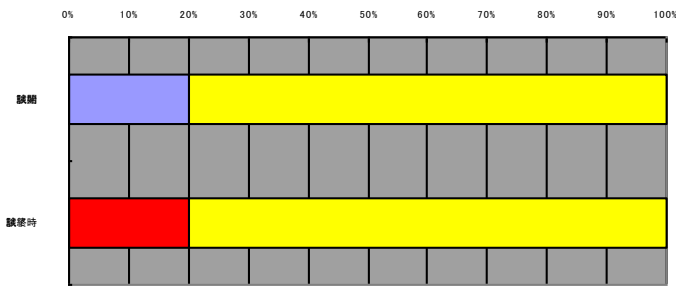
When change in day/night reversal of the placebo subjects was surveyed using Wilcoxon signed-rank test, no significant difference ($p > 0.05$) was observed at the completion of the study compared to the start of the study.

Figure 6. Change in day/night reversal over time (placebo)



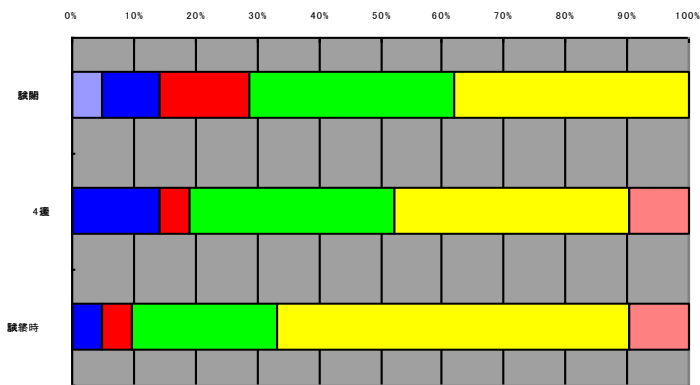
When change in wandering was surveyed using Wilcoxon signed-rank test, no significant difference ($p > 0.05$) was observed at 4 weeks and at the completion of the study compared to the start of the study.

Figure 7. Change in wandering over time



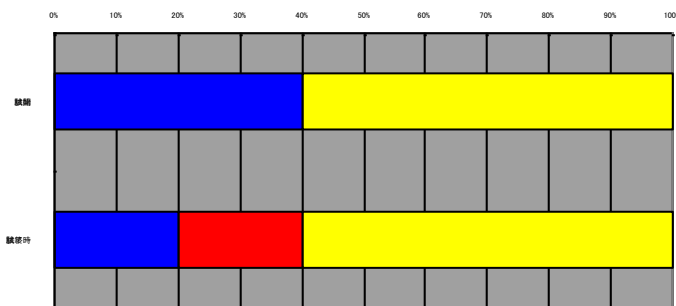
When change in wandering of the placebo subjects was surveyed using Wilcoxon signed-rank test, no significant difference ($p>0.05$) was observed at the completion of the study compared to the start of the study.

Figure 8. Change in wandering over time (placebo)



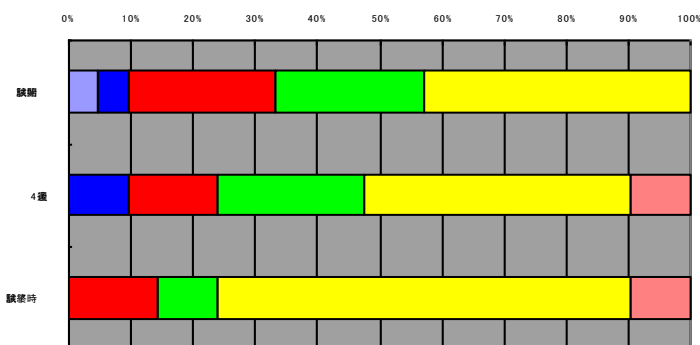
When change in hallucination was surveyed using Wilcoxon signed-rank test, a significant difference ($p<0.05$) was observed at 4 weeks and at the completion of the study compared to the start of the study.

Figure 9. Change in hallucinations over time



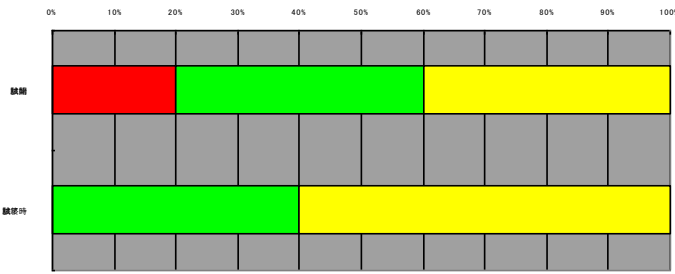
When change in hallucinations of the placebo subjects was surveyed using Wilcoxon signed-rank test, no significant difference ($p>0.05$) was observed at the completion of the study compared to the start of the study.

Figure 10. Change in hallucinations over time (placebo)



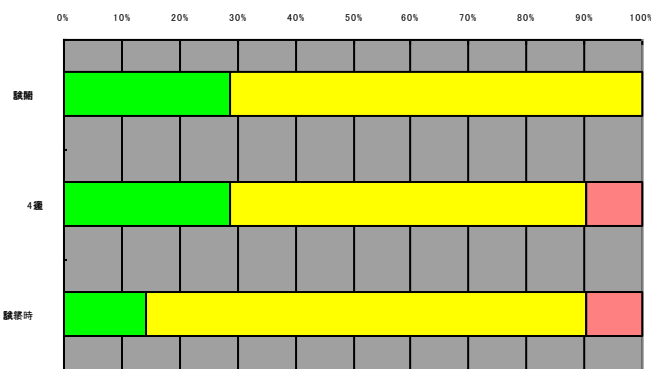
When change in delusions was surveyed using Wilcoxon signed-rank test, a significant difference ($p<0.005$) was observed at 4 weeks and at the completion of the study compared to the start of the study.

Figure 11. Change in delusions over time



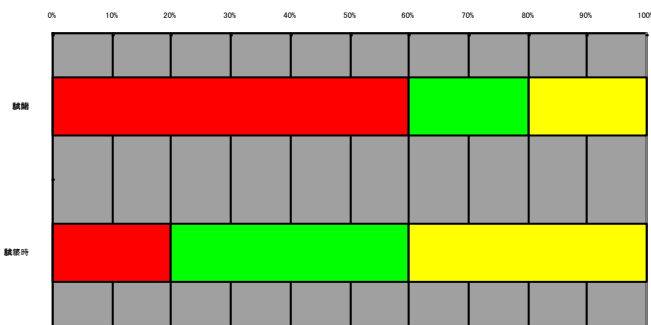
When change in delusions of the placebo subjects was surveyed using Wilcoxon signed-rank test, no significant difference ($p>0.05$) was observed at the completion of the study compared to the start of the study.

Figure 12. Change in delusions over time (placebo)



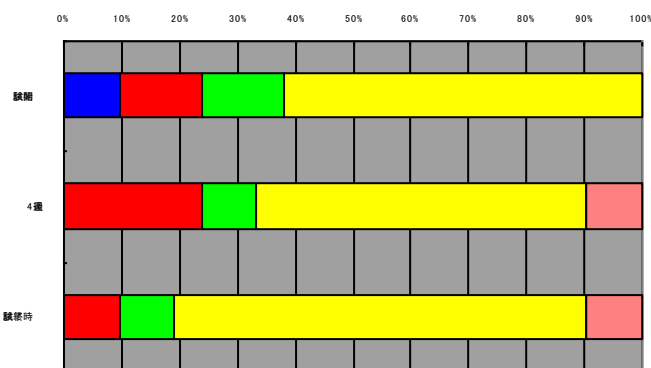
When change in manic depression was surveyed using Wilcoxon signed-rank test, no significant difference ($p>0.05$) was observed at 4 weeks and at the completion of the study compared to the start of the study.

Figure 13. Change in manic depression over time



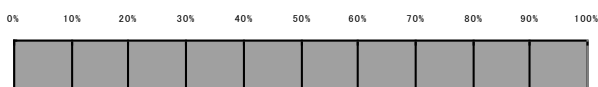
When change in manic depression of the placebo subjects was surveyed using Wilcoxon signed-rank test, no significant difference ($p>0.05$) was observed at the completion of the study compared to the start of the study.

Figure 14. Change of manic depression over time (placebo)



When change in abusive speech and behavior was surveyed using Wilcoxon signed-rank test, a significant difference ($p<0.05$) was observed at 4 weeks and at the completion of the study compared to the start of the study.

Figure 15. Change in abusive speech and behavior over time



When change in abusive speech and behavior of the placebo subjects was surveyed using Wilcoxon signed-rank test, no significant difference ($p>0.05$) was observed at the completion of the study compared to the start of the study.

Figure 16. Change in abusive speech and behavior over time (placebo)

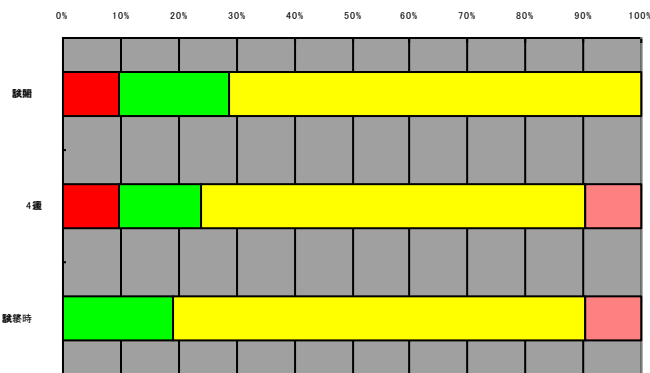


Figure 17. Change in unclean behavior over time

When change in unclean behavior was surveyed using Wilcoxon signed-rank test, a significant difference ($p<0.05$) was observed at 4 weeks and at the completion of the study compared to the start of the study.

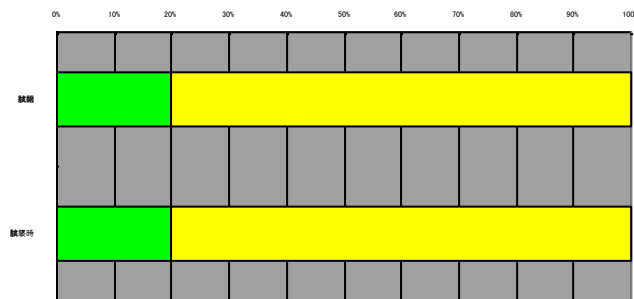


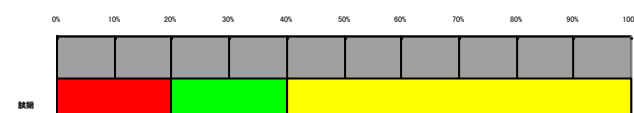
Figure 18. Change in unclean behavior over time (placebo)

When change in unclean behavior of the placebo subjects was surveyed using Wilcoxon signed-rank test, no significant difference ($p>0.05$) was observed at the completion of the study compared to the start of the study.



Figure 19. Change in resistance to nursing care over time

When change in resistance to nursing care was surveyed using Wilcoxon signed-rank test, no significant difference ($p>0.05$) was observed at 4 weeks and at the completion of the study compared to the start of the study.



When change in resistance to nursing care of the placebo subjects was surveyed using Wilcoxon signed-rank test, no significant difference ($p>0.05$) was observed at the completion of the study compared to the start of the study.

Figure 20. Change in resistance to nursing care over time (placebo)

C. Side effects

7 cases, 21% overall, discontinued participation after the start of the study due to side effects or were unable to continue participation. Reasons for discontinuation in 7 cases are shown in Table 3.

Table 3 Reasons for discontinuation in 7 cases, No. of days from the start

Case	Symptoms	No. of days from the start
KM	difficulty taking medicine	1 week later
YT	difficulty taking medicine	1 week later
IR	difficulty taking medicine	4 weeks later
KT	difficulty taking medicine	4 weeks later
WY	difficulty taking medicine	4 weeks later
IM	severe pollakiuria	4 weeks later
KH	difficulty taking medicine	4 weeks later

D. Blood test

In order to consider anti-aging, clinically significant IGF-I and DHEA-S were measured and considered.

1. Study subjects and placebo subjects (control)

(1) IGF-I

IGF-I is a substance that performs intermediate action on growth hormones over a wide area, including growth promotion, insulin-like activity, cell growth, etc. In addition, it is considered as an evaluation of GH secretory capacity since its concentration decreases with age. Blood concentration of IGF-I was measured at the blood test, and statistically considered.

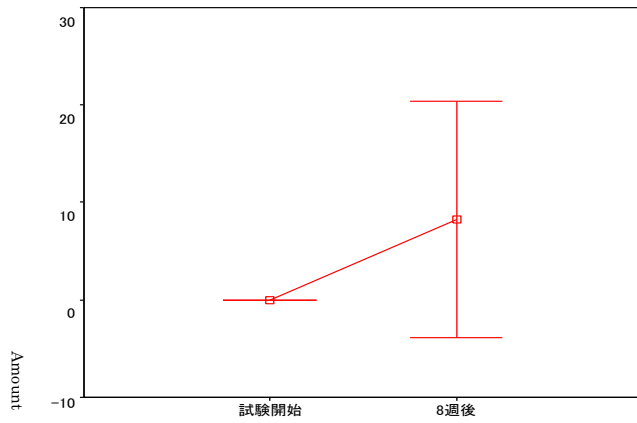


Figure 21. Change in IGF-I over time

When change in IGF-I value of the study subjects was surveyed using Wilcoxon signed-rank test, no statistical significant difference ($p>0.05$) was observed.

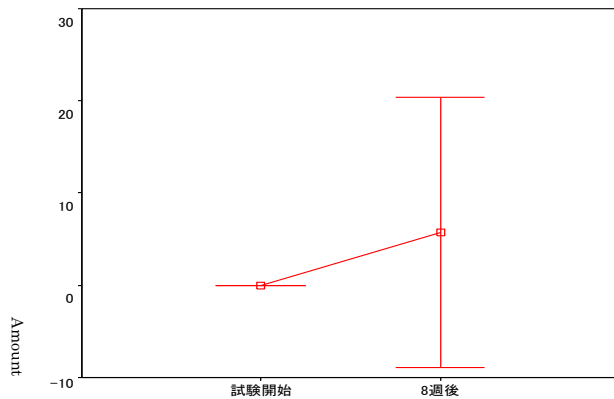


Figure 22. Change in IGF-I over time (placebo)

When change in IGF-I value of the placebo subjects was surveyed using Wilcoxon signed-rank test, no statistical significant difference ($p>0.05$) was observed.

(2) DHEA-S

It has called as adrenal androgen, and noticed as indicator showing biological function in viewpoint of controlling aging. Elderly with dementia have reduced DHEA-S value more than healthy persons. Moreover, DHEA-S is reduced as getting older after peak of around 20 year old. Blood concentration of IGF-I was measured at the blood test, and statistically considered.

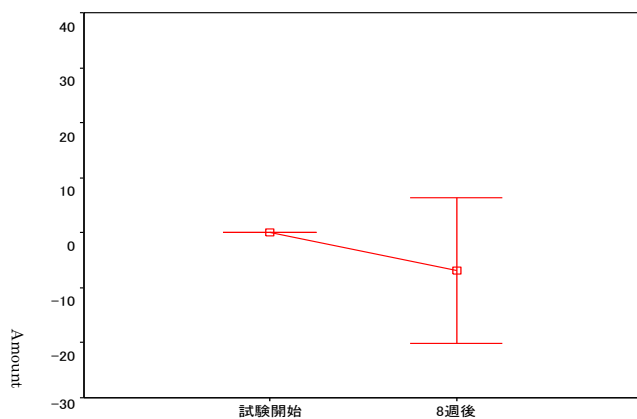


Figure 23. Change in DHEA-S over time

When change in DHEA-S value of the study subjects was surveyed using Wilcoxon signed-rank test, no statistical significant difference ($p>0.05$) was observed.

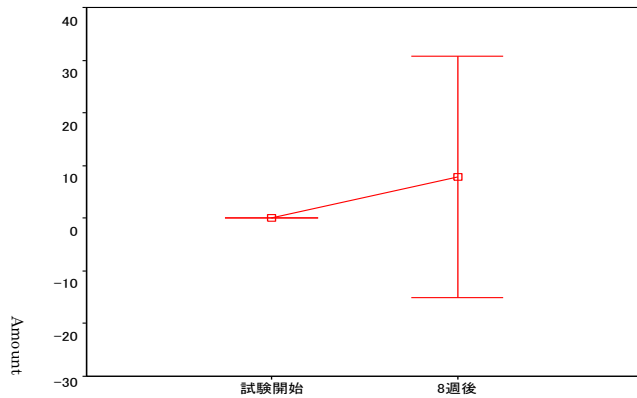


Figure 24. Change in DHEA-S over time (placebo)

When change in DHEA-S value of the placebo subjects was surveyed using Wilcoxon signed-rank test, no statistical significant difference ($p>0.05$) was observed.

2. Difference in Change by age

(1) IGF-I

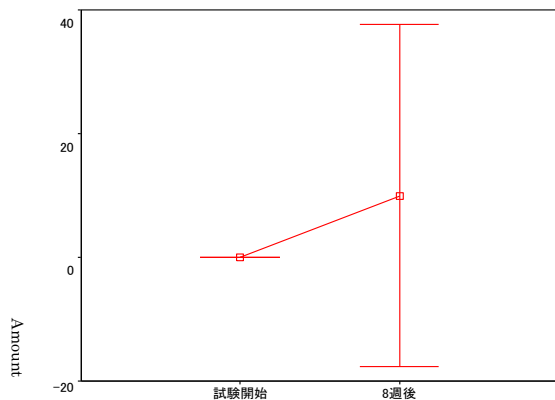


Figure 25. Change in IGF-I values in advanced elderly over time

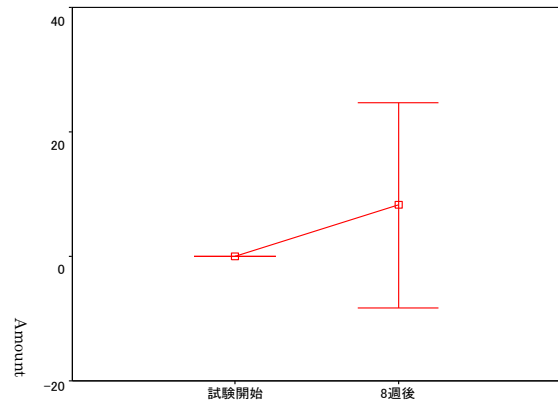


Figure 26. Change in IGF-I values in super advanced elderly over time

When surveyed using Wilcoxon signed-rank test, no statistical significant difference ($p>0.05$) was observed for either the advanced elderly group (75-84 years) or the super advanced elderly group (85 years and older).

(2) DHEA-S

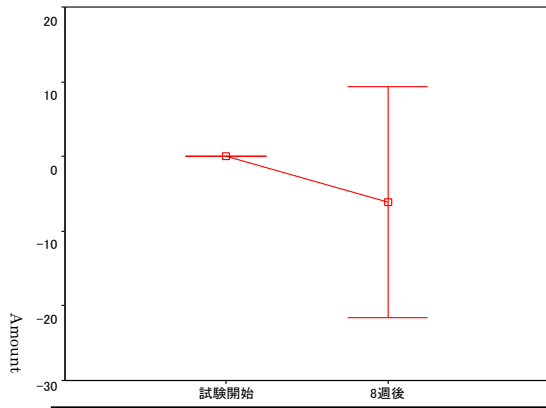


Figure 27. Change in DHEA-S values in advanced elderly over time

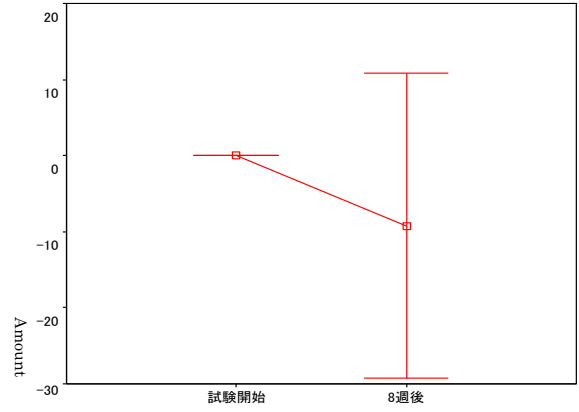


Figure 28. Change in DHEA-S values in super advanced elderly over time

When surveyed using Wilcoxon signed-rank test, no statistical significant difference ($p > 0.05$) was observed for either the advanced elderly group (75-84 years old) or the super advanced elderly group (85 years and older).

3. When subjects with complications are excluded

(1) IGF-I

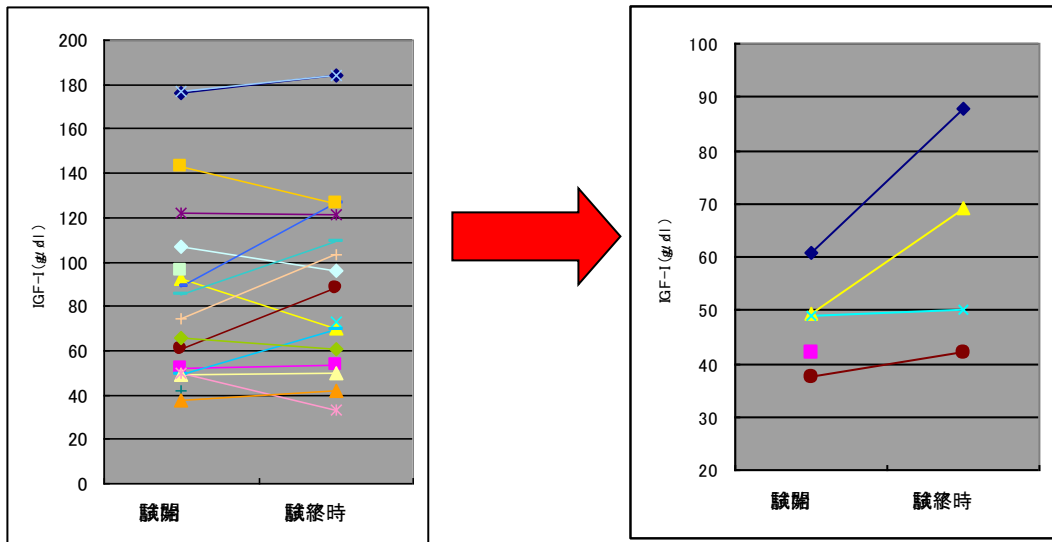


Figure 29. Change in the group with lower IGF-I values over time (excluding persons with complications)

(2) DHEA-S

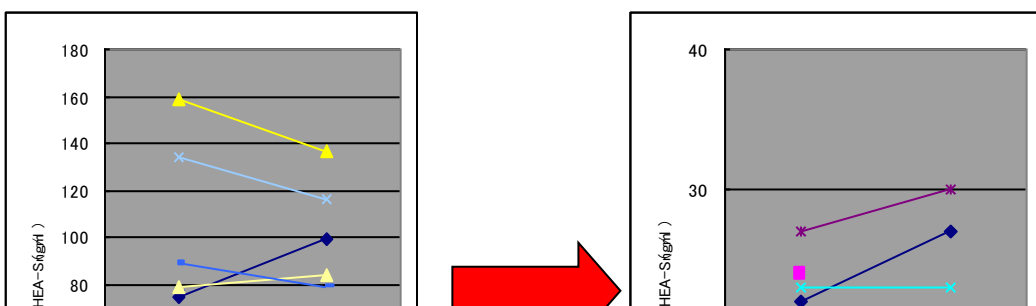


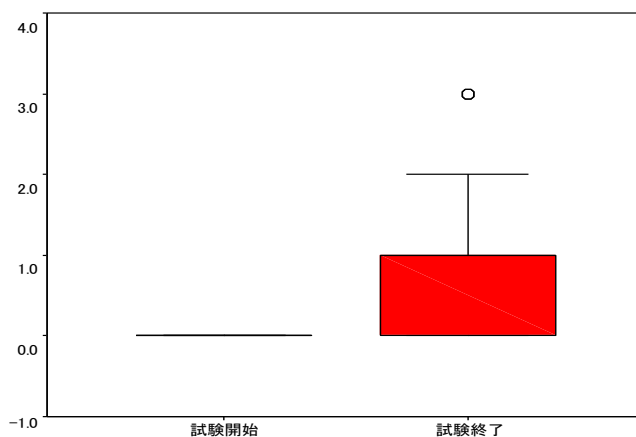
Figure 30. Change in the group with lower DHEA-S values over time (excluding persons with complications)

According to the results at this time, when persons with lower IGF-I, DHEA-S were extracted, all in this group, excluding patients with diabetes and kidney failure, were thought to show an improving tendency.

E. Satisfaction Level

Satisfaction in the study subjects (excluding placebo subjects) and satisfaction by age were surveyed.

1. Study subjects



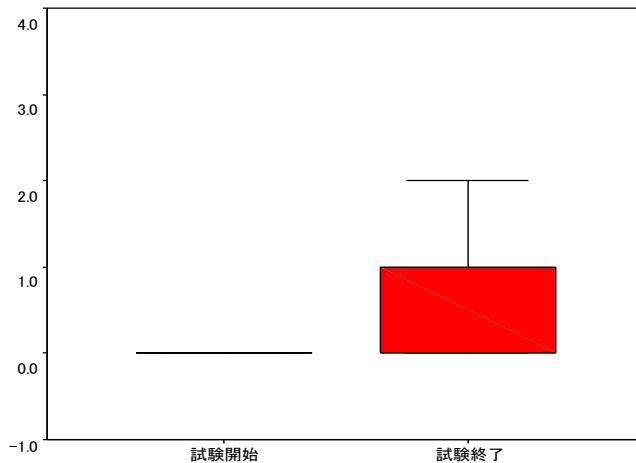
The following numerical conversion was performed and analyzed.

- 3= very good
- 2= good. Recommend to others
- 1=good. Not inclined to recommend to others
- 0= I don't know
- 1= better not to have tried it

When change in satisfaction of the study subjects was considered using Wilcoxon signed-rank test, significant increase in satisfaction ($p < 0.005$) was observed at the completion of the study compared to the start of the study.

2. Difference in Effect by Age

(1) Satisfaction in the advanced elderly group (75-84 years old)



The following numerical conversion was performed and analyzed.

3= very good

2= good. Recommend to others

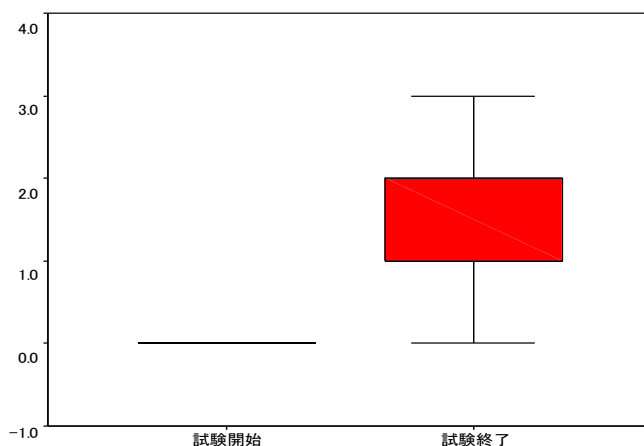
1=good. Not inclined to recommend to others

0= I don't know

-1= better not to have tried it

When change in satisfaction of the advanced elderly group was considered using Wilcoxon signed-rank test, increase in satisfaction was observed at completion of the study compared to the start of the study. However, no statistical significant difference ($p>0.05$) was observed.

(2) Satisfaction in the super advanced elderly group (85 years and older)



The following numerical conversion was performed and analyzed.

3= very good

2= good. Recommend to others

1=good. Not inclined to recommend to others

0= I don't know

-1= better not to have tried it

When change in satisfaction of the super advanced elderly group was considered using Wilcoxon signed-rank test, a significant increase in satisfaction ($p<0.05$) was observed at the completion of the study compared to the start of the study.

Discussion

This test product, which is a combination of natural herbs and promotes activation in the living body, was administered to patients with dementia, and clinical efficacy and safety were considered.

According to the intellectual function test by MMSE (mini mental state examination), a significant difference was observed in the study subjects from 4 weeks after the start of the study, and a significant difference was even observed 8 weeks later. Meanwhile, in the placebo subjects, no special significant difference was shown. According to these facts, this test product is thought to be able to provide efficacy in the intellectual function test for dementia.

In daily life self-supported degree judgment survey in problem behaviors, 5 items (day/night reversal, hallucination, delusion, abusive speech and behavior, and unclean behavior) within 8 items showed especially significant difference. Meanwhile, in placebo subjects, no special significant difference was shown. According to these facts, this test product is thought to be able to provide efficacy in daily life self-supported degree judgment survey for dementia.

For the survey on anti-aging by blood test, IGF-I (somatomedin C) and DHEA-S (dehydroepiandrosterone sulfate), which are considered to be closely related to clinical states frequently occurring in elderly and which have gained attention, were measured and verified. As a result, no statistical significant difference was observed in this study.

Regarding discontinuation due to side effects, most cases of discontinuation received a larger daily dose of the test product, and most of these subjects asked to discontinue because they could not take the entire dose. Only one case was discontinued due to severe pollakiuria, but this was a result of a worsening pre-existing condition, and administration was discontinued immediately in consideration of appropriate safety. Due to these reasons, discontinuation rate was 21%. Consequently, it is considered that there are no specific concerns regarding normal administration.

According above results, a statistical significant difference of intellectual function improvement and self-supported degree in daily life were observed with the use of the compound drug (Kippogen) which natural herbs are its main ingredient. This test product is considered useful as adjuvant therapy for dementia.

Description of the statistical method

Wilcoxon signed-rank test

In principle, the Wilcoxon signed-rank test method is a non-parametric statistical hypothesis test to determine whether a numerical sample is equal to a specified median value of the parent group, and is explained using mathematical signs. In particular, Wilcoxon signed-rank test is used to calculate the difference between two opposite measurement values, and to carry out definite statistical consideration.