

An Effectiveness Study of Hyaluronic acid [Hyabest® (J)] in the Treatment of Osteoarthritis of the Knee on the Patients in the United States

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Abstract :

Patients of knee osteoarthritis are also increasing in other area than Japan. In the United States, for instance, number of the patients are estimated to reach 21 million, however so far there are no study reports available on the effectiveness of oral intake of hyaluronic acid for the American patients. We have conducted a placebo controlled double blind test on 37 patients, who were age 40 or above and lived in the United States, by orally feeding them with 200mg/day of high purity hyaluronic acid (Hyabest® (J)) for 8-weeks. Effectiveness in the reduction of pain in the knee joints was assessed by the changes in WOMAC (Western Ontario McMaster universities Osteoarthritis Index) scores. At the same time safety of the oral intake of Hyabest (J) was examined by blood tests conducted at pre-and-aft administration.

Significant improvement in WOMAC scores was observed after 4-weeks of oral intake in the group of Hyabest (J). As the group of placebo also showed decline in WOMAC scores there was no statistically significant differences observed between the two groups. However, in the analysis of the scores of patients only suffering from severe pain the Hyabest (J) group has shown significant improvement over the placebo group. No adverse changes for safety were detected from the blood test readings. The above study result suggests that oral intake of high purity hyaluronic acid (Hyabest (J)) is effective in the treatment of American patients of knee osteoarthritis.

Key words : Hyaluronic acid, American patients, knee osteoarthritis, double blind test, test by oral intake

I. Preface

As the population of senior citizens has been increasing, number of knee osteoarthritis patients who are suffering from degeneration in the joint cartilage or in the subcartilaginous bone tissue with pain, tenderness or inflammation has been sharply rising. It is reported that in the United States currently about 40% of the population of age 60 or elder have some symptoms and about 10% are complaining of difficulties in their daily life ¹⁾.

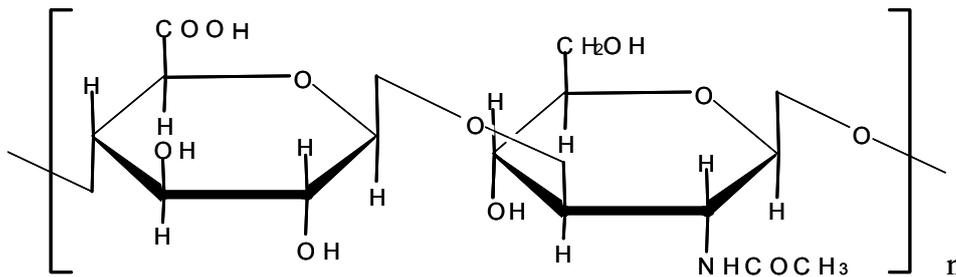


Fig. 1. Chemical structure of Hyaluronic acid

Joint cartilages are composed of type II collagen and proteoglycan containing hyaluronic acid, and synovial fluid filling joint cavity contains hyaluronic acid secreted from synovial membrane ²⁾. It has been confirmed that hyaluronic acid level particularly in synovial fluid decreased by aging ³⁾. Hyaluronic acid is a kind of high molecular poly-saccharides with tens of thousands to millions of molecular weight, having linear structure of N-acetyl-glucosamine and D-glucuronic acid alternate chains (Fig. 1.). It is known that direct injection of hyaluronic acid to joint cavity improves symptom of osteoarthritis and it is now commonly used for injection to the patient's joints.

The writers have already published a report concerning a human test conducted in Japan, and confirmed the effectiveness of oral intake of 240 mg/day high purity hyaluronic acid (Hyabest (J)) in the treatment of knee osteoarthritis ⁴⁾.

While number of patients of knee osteoarthritis has also been increasing in the western society and it is estimated to have reached 21 mil. in the United States only ⁵⁾, so far no reports on the test result of oral intake of hyaluronic acid to American patients of knee osteoarthritis are available. Now we have conducted placebo controlled test of 8-weeks oral intake of Hyabest(J) on American patients with knee osteoarthritis for

the assessment of its effectiveness. Since our previous test conducted in Japan with 240mg/day dose has clearly demonstrated effectiveness of oral intake of Hyabest(J) in the treatment of knee osteoarthritis, we have carried out the test with reduced dose of 200mg/day of Hyabest(J) this time.

II. Target subjects

Test subjects are male and female patients with knee osteoarthritis at their age 40 or elder and are living in the States, who are at the same time classified into the grade II or III of Kellgren-Lawrence classification by the radio-graph. In the meantime informed consent by the subjects were obtained in writing at the time of screening and only those who confirmed their consent to participate in the test were enrolled in the program.

The test was conducted after its protocol and relevant documents were evaluated and approved by the institutional review board in San Diego, and after written consent of each subject was obtained after providing them individually with full explanation of the test program prior to the test, in compliance with the Principle of Helsinki Declaration.

Table 1. Analysis of Hyabest(J)
(%)

| Ingredient | Analytical value |
|-----------------|------------------|
| Protein | 0.01 |
| Fat | 0.01 |
| Hyaluronic acid | 98.49 |
| Moisture | 1.49 |

III. Test methods

1. Test sample (food)

Analysis result of high purity Hyaluronic acid (Q.P.Corp. product name: Hyabest(J)) made by microbial fermentation method is exhibited in Table 1.

3-hard capsules of test sample which in total contains 200mg of Hyabest(J) and cornstarch were fed after breakfast to each subject of Hyabest(J) Group, while apparently identical 3-capsules but in which Hyabest(J) was substituted with

cornstarch were given to each subject of Placebo Group after breakfast. In view of religious reasons hard capsules were all made of vegetable materials.

2. Test design and test period

The test was programmed as placebo controlled double blind test and conducted for the period of 8-weeks. 3-observation time points were programmed; pre-administration, 4-weeks of administration and 8-weeks of administration.

Table 2. List of questionnaires by WOMAC

Section A Pain

Based on your experience in the last 48 hours, state the degree of pain which you felt in each action shown below.

1. Walking on level place
 2. Ascending or descending stair way
 3. While sleeping (pain interrupting your sleep)
 4. Sitting down or laying down
 5. Standing straight
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Section B Stiffness

Based on your experience in the last 48 hours, state the degree of stiffness (not pain but stiff feeling in the knee which makes movement of the joint uneasy) which you felt in each action shown below.

6. Stiffness you feel when you wake up in the morning.
 7. Stiffness you feel in the daytime when you sit down, laying down or after resting a while.
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Section C Difficulties in the Daily Living

State the degree of difficulties which you felt in each of the following action.

8. Descending stairway
9. Ascending stairway
10. Standing up from sitting position on a chair
11. Standing still
12. Crouching down to pick something on a floor up
13. Walking on level place
14. Stepping in or out from a car or a bus
15. Going out for shopping
16. Putting socks or stockings on by yourself
17. Sitting up from a bed
18. Taking socks or stockings off by yourself
19. Stay laying down on a bed
20. Going in a bathtub or coming out of bathtub
21. Sitting down on a chair
22. Using toilet (a stool)
23. Doing heavy housework (like cleaning the floor, carrying heavy stuff or wiping the floor)
24. Doing light housework (like tidying up own belongings or cleaning up a dining table)

3. Method of assessment

Assessment at each time point was made according to the scoring of WOMAC (Western Ontario McMaster universities Osteoarthritis Index)⁶. Questionnaires in the WOMAC scoring are listed in Table 2. There are 5 questionnaires relevant to “Pain”, 2 to “Stiffness” and 17 to “Difficulties in the activities of Daily Living (hereafter stated as “ADL”)” and point 0 represents lightest symptom and point 4 the severest symptom for each questionnaire. That means total score of the severest symptom for “Pain” will be 20, for “Stiffness” will be 8 and for “ADL” will be 68 and consequently “Total” will be 96. Score for each category and for “Total” will decline when the symptom is improved. Differences in the score between pre-administration and two other time points, also between Hyabest Group and Placebo Group were analyzed for assessment.

4. Blood test

Safety of the oral intake of Hyabest (J) was assessed by blood tests conducted twice, at pre-administration and on completion of the test (8-weeks). Test items are: blood cell's components (white cell count, red cell count, hemoglobin and hematocrit) , urea nitrogen, creatinine, AST(GOT), ALT(GPT), alkaline phosphatase, blood sugar level, sodium and potassium.

5. Methods of statistical processing

Within-group comparison of WOMAC scores for each category and the total score was tested by Wilcoxon's signed rank test (with multiple comparison by Bonferroni's inequality) and between-groups comparison of the same was tested by Mann-Whitney's U-test. Within-group comparison of blood test results was tested by paired t-test and between-groups comparison by unpaired t-test. Dr.SPSS II for Windows by SPSS Co., Ltd. was used as statistical software and significant level for each test was set at risk less than 5%.

IV. Test result

1. Test subjects

The test was commenced with 40 potential subjects, but 3 were failed due to personal reasons and finally total 37 subjects were enrolled into the test, of which 20 were assigned to Hyabest Group and 17 to Placebo Group. Demographic characteristic of 37 subjects (8-males and 29-females) are exhibited in Table 3

Table 4. Changes in WOMAC scores

| | | (Points) | | |
|-----------|--------------------|---------------|-------------|-------------|
| | Group | Pre-administ. | 4-weeks | 8-weeks |
| Pain | Hyabest (J) Group | 10.7 ± 1.1 | 8.3 ± 1.0* | 6.2 ± 1.0* |
| | Placebo Group | 10.6 ± 0.8 | 7.1 ± 0.9* | 6.5 ± 1.0* |
| Stiffness | Hyabest (J) Group | 4.8 ± 0.4 | 3.3 ± 0.4* | 2.8 ± 0.5* |
| | Placebo Group | 4.7 ± 0.4 | 3.2 ± 0.4* | 3.2 ± 0.5* |
| ADL | Hyabest (J) Group | 40.3 ± 3.5 | 28.8 ± 3.1* | 22.4 ± 3.6* |
| | Placebo Group | 38.5 ± 2.2 | 26.3 ± 3.1* | 24.6 ± 3.1* |
| Total | Hyabest (J) Group | 55.7 ± 4.9 | 40.4 ± 4.4* | 31.3 ± 5.1* |
| | Placebo Group | 53.9 ± 3.1 | 36.5 ± 4.3* | 34.4 ± 4.5* |

Mean +/- Standard error

*: P < 0.05 vs Pre-administration

2. Assessment by WOMAC scoring

Changes in the WOMAC score for each assessment category are shown in Table 4. Significant decrease of the scores were observed at 4-weeks and afterwards in both Hyabest(J) Group and Placebo Group. Although no statistically significant difference was observed between Hyabest (J) Group and Placebo Group, mean score of each assessment category at 8-weeks was smaller in Hyabest(J) Group.

3. Blood test

Compared with the pre-administration readings, statistically significant increase of alkaline phosphatase and decrease of ALT (GPT) both in Placebo Group and significant decrease of white blood cell count in both Groups were observed at 8-weeks time point, however these were not such as clinically important. Thorough-out the whole test period there were no significant changes between Hyabest(J) Group and Placebo Group nor any adverse event attributable to the test sample.

V. Consideration

Effectiveness of oral intake of Hyabest(J) in the treatment of knee osteoarthritis of American patients was assessed by WOMAC scoring. Significant improvement of the scores was observed in Hyabest(J) Group at 4-weeks time point and afterwards compared with pre-administration. On the other hand ,significant improvement in the scores was also observed in Placebo Group at 4-weeks and afterwards ,which indicates no significant differences existed between Placebo Group and Hyabest Group. However, mean of the scores at 8-weeks of Hyabest Group was smaller than that of Placebo Group.

NIH (National Institutes of Health) has conducted a study on efficacy of oral intake of Glucosamine and Chondroitin sulfate together on knee osteoarthritis assessed by WOMAC index. In this study there reported no significant differences between the test group and the placebo group , however in the strata analysis of two groups, patients with low scores in “Pain” and those with high scores it was reported that intake of glucosamine and chondroitin sulfate was effective to alleviation of adverse symptom of osteoarthritis⁷⁾. In view of the outcome of this study we have also made stratum analysis targeting at the test subjects with not less than 10 score of “Pain”.

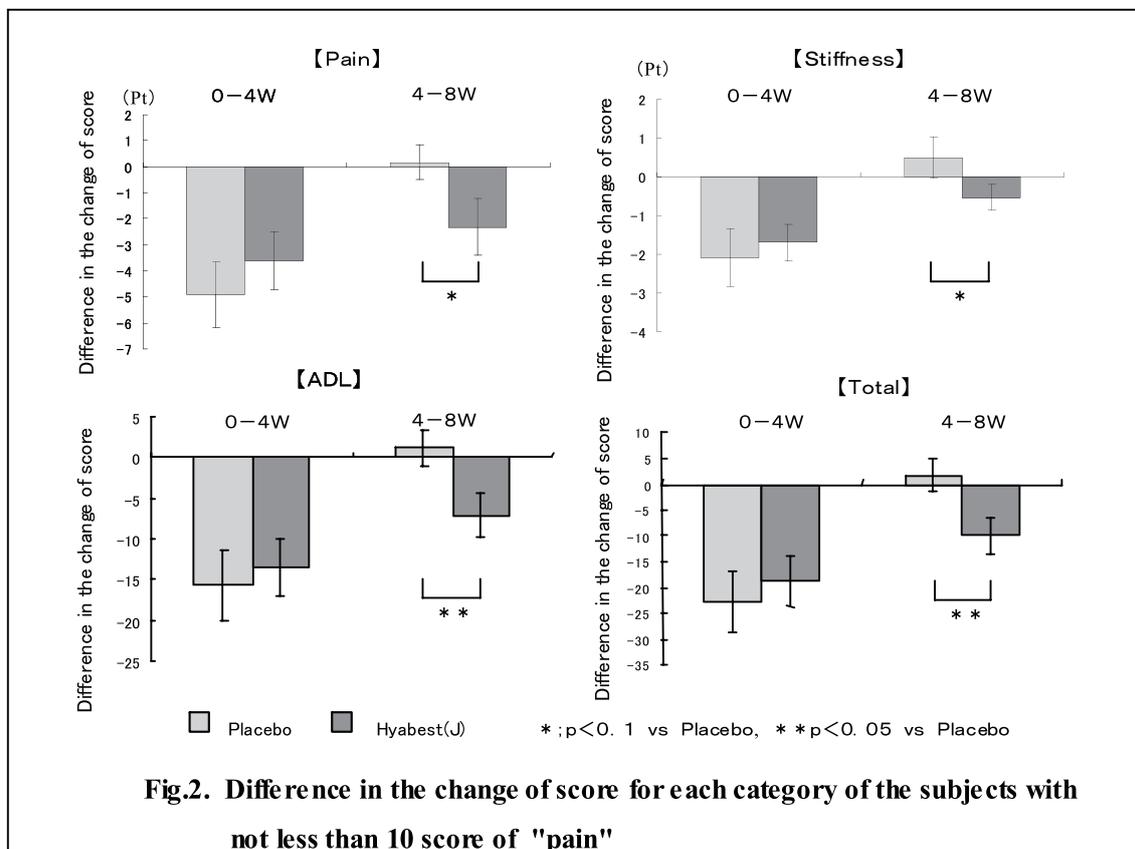


Fig.2. Difference in the change of score for each category of the subjects with not less than 10 score of "pain"

The target stratum consisted of 13 subjects of Hyabest Group and 12 of Placebo Group. In consideration of the influence of placebo effects which is deemed to be evident for the initial period up to 4-weeks, we have assessed “the scores between pre-administration and 4-weeks” and “4-weeks and 8-weeks”. Minus score means improvement in symptoms. The changes are exhibited in Fig. 2. Comparison of the scores of two groups tested by Mann-Whitney’s U-test showed significant improvement in Hyabest(J) Group against Placebo Group for “ADL” and “Total” scores in “4-weeks and 8-weeks” though no significant differences were seen in “the score between pre-administration and 4-weeks”. Also the analysis showed improving tendency for “Pain” and “Stiffness” in Hyabest(J) Group against Placebo Group.

The above strata analysis suggests that at 4-weeks and afterwards oral intake of Hyabest(J) is effective in the treatment of knee osteoarthritis of American patients, though in the initial 4-weeks period no significant differences were observed between Hyabest(J) Group and Placebo Group possibly due to the influence of placebo effects.

The writers of this report have already made a human trial of oral intake of Hyabest (J) 240mg/day on Japanese patients of osteoarthritis and reported its effectiveness in the improvement of the symptom⁴⁾. From the test result on American patients this time which also suggested improvement of symptom of knee osteoarthritis, it is deemed that Hyabest(J) is a food material with which improvement of the symptom is expected at 200mg/day dose level.

Direct injection of hyaluronic acid into joint cavity is commonly used for the treatment of knee osteoarthritis and inhibition of cartilaginous degeneration⁸⁾, protection of cartilaginous surface⁹⁾, normalization of synovial fluid level¹⁰⁾ and alleviation of pain by various anti-inflammatory action¹¹⁾ are known. Although action mechanism in the improvement of knee osteoarthritis by oral intake of Hyabest (J) has not been clarified yet, the test result confirming effectiveness in the improvement of the symptom in rather short period of 4-weeks of the intake suggests that its anti-inflammatory multi-function contributes to the effectiveness.

Oral intake of Hyabest (J) is expected to contribute to reducing burden of “regular visit to specialized institute” or of “side-effects of medicine” on the patients which are the important issues of currently prevailing major treatments of knee osteoarthritis; physiotherapy, pharmacotherapy and orthotherapy.

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