The effect of oral low molecular weight liquid hyaluronic acid combination with glucosamine and chondroitin on knee osteoarthritis patients with mild knee pain

An 8-week randomized double-blind placebo-controlled trial

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Abstract
Background: The popularity of dietary supplements for knee osteoarthritis (OA) management is on the rise; however, their effects are still debated.

Methods: This study aimed to investigate the effect of an oral low molecular weight liquid hyaluronic acid supplement in the treatment of knee OA patients with mild knee pain (visual analogue scale [VAS] ≤3) in Taiwan population. This was a randomized, double-blind, placebo-controlled study. Forty-seven subjects were enrolled and randomly allocated to either the A+HA or the placebo groups. The subjects were required to drink a bottle contained 20 mL of A+HA or placebo daily throughout an 8-week study period. The efficacy was assessed by using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the 36-item Short Form Survey (SF-36).

Results: At Week 8, significant reductions from baseline in the WOMAC pain (−2.6 ± 1.68, P < .0001), stiffness (−1.2 ± 1.50, P = .007), physical function (−5.8 ± 4.39, P < .0001), and total (−9.4 ± 5.82, P < .0001) scores were observed in the A+HA group but not in the placebo group. Significant differences in the mean change of WOMAC scores from baseline at Week 8 between groups were detected (P < .01). At Week 8, the A+HA group also showed significant improvements in SF-36 physical functioning (2.7 ± 3.10, P = .001) and bodily pain (0.7 ± 1.50, P < .05) domains. Although the A+HA group had a higher increase in the SF-36 total score than the placebo group but the difference was not statistically significant (2.1 ± 12.75 vs 0.3 ± 19.66, P = .12).

Conclusions: Oral administration of low molecular weight liquid HA appeared to be effective for knee OA patients with mild knee pain (VAS ≤3) in the relief of knee OA symptoms, particularly in pain and physical function.

Clinical Trial Registration: NCT04352322.

Abbreviations: HA = hyaluronic acid, OA = osteoarthritis, QoL = quality of life, SF-36 = 36-item Short Form Survey, VAS = visual analogue scale, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Keywords: knee osteoarthritis, oral liquid hyaluronic acid, quality of life, Western Ontario and McMaster Universities Osteoarthritis Index.

1. Introduction

Osteoarthritis (OA) of the knee is a degenerative joint disease with its occurrence ascends with age in the adult population. It characterized by a gradual breakdown of the knee articular cartilage especially in the weight bearing area and a reduction in viscoelasticity of the synovial fluid which ultimately leads to disability.[1] It is a disease with no complete cure currently and the treatments available primarily focus on the relief of symptoms and delay of the disease progression.

Being the main component in and the contributor to the viscosity of synovial fluid,[2] visco-supplementation of oral low molecular weight hyaluronic acid (HA) or intra-articular
injection of high molecular weight HA is one of the treatment option for knee OA. The high molecular weight HA for intraarticular injection has been approved in various countries since 1987 as an indication for the treatment of pain in knee OA patients who have failed response adequately to nonpharmacologic therapy, non-steroidal anti-inflammatory drugs or analgesics. Despite its proven efficacy and safety, some patients might still hesitate for the intraarticular injection of high molecular HA because of the discomfort associated with multiple injections and the necessity for repeatedly clinic visits. To overcome the above mentioned disadvantages, oral administration of low molecular weight HA which can be absorbed in the gastrointestinal tract would be a desirable way.

The efficacy of low molecular weight HA ingestion in knee OA has been investigated in several studies and the results remain controversial. For instance, Sato and Iwasso and Kalman et al did not observe a significant difference in the reduction of Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) score between the oral HA and the placebo groups during the 8-week study period. While, Nelson et al found that the oral HA group was significantly superior to placebo group in both WOMAC score (27.62 ± 4.38 vs 39.58 ± 3.97, P < 0.5) and visual analogue scale (VAS) pain score (4.06 ± 0.53 vs 5.84 ± 0.50, P < 0.05) at 12 weeks. Also, in a study comparing the efficacy of injection and ingestion of HA in early knee OA, significant improvements were demonstrated in both treatment groups as assessed by the American Knee Society Score and VAS for pain at 3 months.

To address the above mentioned issues as well as to collect relevant data in Taiwan population, we conducted a study to investigate the efficacy of an oral low molecular weight liquid HA in the relief of symptoms and improvement of the quality of life (QoL) in patients with knee OA and had mild knee pain symptom.

2. Methods

2.1. Study design

This was a randomized, double-blind, placebo-controlled, 8-week study designed to evaluate the effectiveness of oral low molecular weight A+HA (TOP Pharm & Medicalware, Taiwan) for symptom relief and improvement QoL in Taiwanese knee OA patients. The A+HA is a 20mL liquid combination supplement containing 50mg of HA with low molecular weight (5 × 10^5–5 × 10^5 Da), 750mg of glucosamine, and 250mg of chondroitin. The placebo was a 20mL oral solution with similar appearance and odor as the study product but contained no active ingredient. Both the study product and the placebo were manufactured and provided by TOP Pharm. & Medicalware, Taiwan. All eligible subjects were instructed to administer a bottle of study product or placebo once daily in the morning under fasting condition for a period of 8 weeks.

2.2. Ethics

This was a single center study took place in China Medical University Hospital under the approval of China Medical University and Hospital Research Ethics Committee (DMR101-IRB2-033) and conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All subjects gave and signed their informed consents for the study participation.

2.3. Eligibility

Male or female age ≥40 years, diagnosed with knee OA which met the definition of Ahlbäck classification and had knee joint symptoms within 30 days prior to enrollment were eligible. Subjects were excluded from this study if they had administered glucosamine 1 month prior to enrollment, known allergy to oral HA, body mass index ≥240kg/m^2, or their knee OA was caused by occupational hazard or sports injury. Patients with known other causes of arthritis (infectious rheumatoid or psoriatic arthritis), bony or soft tissue malignancy or peripheral neuropathy involving the lower extremities, cardiopulmonary disease which limited walking more than knee pain, knee instability defined as a report of knee buckling or locking within the past month of the study knee, major neurological deficit that affected gait, psychiatric illness that limited informed consent or Parkinsonism were excluded too. Women in pregnancy and wheel chair users were also excluded.

2.4. Interventions

The study product, A+HA mixture, was a 20mL oral solution containing a mixture of 50mg HA (5 × 10^5–5 × 10^5 Da), 750mg glucosamine, and 250mg chondroitin. The placebo was a 20mL oral solution with similar appearance and odor as the study product but contained no active ingredient. Both the study product and the placebo were manufactured and provided by TOP Pharm. & Medicalware, Taiwan. All eligible subjects were instructed to administer a bottle of study product or placebo once daily in the morning under fasting condition for a period of 8 weeks.

2.5. Sample size

The sample size of the study was set based on the feasibility of the study, statistical power calculation was not used in establishing the sample size.

2.6. Randomization and blinding

A permuted block randomization method with a 1:1 ratio was employed to allocate subjects into 1 of the 2 treatment groups. The study conducted in a double-blind manner. Neither the subjects nor the study staffs were aware of the allocation.

2.7. Outcome

The patient’s knee OA symptoms were assessed by the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index. This index consists of 3 subscales, that is, pain (5 items), stiffness (2 items), and physical function (17 items) with a maximum total score of 96. The higher the score, the greater the severity. Meanwhile, the patient's QoL was evaluated by the 36-Item Short Form Survey (SF-36) which covers 8 domains: physical functioning (10 items), role limitations due to physical health (4 items), pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role limitations due to emotional problems (3 items), and emotional well-being (5 items). It also includes a single item that identifies perceived change in health. A higher score indicates a better QoL. A composite score for both WOMAC and SF-36 are calculated by summng all sub-scores of the covered domains.
Over the 8-week study period, the A+HA group showed a gradual improvement in baseline (Table 1).

Baseline demographics and clinical characteristics of all randomized subjects.

|                  | A+HA (n = 24) | Placebo (n = 23) | P value |
|------------------|---------------|------------------|---------|
| Gender (n, %)    | Male 18 (75.0%) 6 (26.1%) | Female 6 (25.0%) 6 (26.1%) | .93     |
| Age, mean±SD, y | 61.5±9.9     | 60.8±10.7  | .71     |
| Weight, mean±SD, kg | 66.9±3.9  | 73.4±29.1  | .79     |
| Height, mean±SD, cm | 161.6±7.9 | 152.2±30.1 | .53     |
| BMI, mean±SD, kg/m² | 25.1±3.10 | 25.7±3.70  | .49     |
| Brief pain inventory (scale 0–10), mean±SD | 2.58±1.25 | 2.65±0.71 | .47     |
| WOMAC scores, mean±SD | 43.2±2.76 | 40.2±2.91 | .58     |
| Pain              | 1.7±1.55     | 1.2±0.98   | .34     |
| Physical function | 9.3±5.91     | 11.5±5.90  | .62     |
| Total             | 15.2±7.70    | 16.7±12.65 | .87     |
| SF-36 scores, mean±SD | 23.2±3.19 | 22.0±5.66  | .72     |
| Physical functioning | 5.3±1.59    | 5.0±1.83   | .65     |
| Role limitations-physical | 8.9±1.73 | 8.6±1.51   | .30     |
| Bodily pain       | 17.7±3.29    | 18.1±2.46  | .88     |
| General health    | 17.4±3.85    | 17.5±3.08  | .85     |
| Vitality          | 8.6±1.58     | 8.5±1.62   | .83     |
| Social functioning | 0.2±0.66    | 0.7±1.18   | .12     |
| Role limitations-emotional | 22.3±3.56 | 22.6±2.68  | .97     |
| Mental health     | 103.7±11.70  | 101.4±16.27 | .76     |

BMI = body mass index, SD = standard deviation, SF-36 = 36-item Short-Form Survey, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

2.8. Statistical analysis

All randomized subjects were included in the statistical analysis. Mann–Whitney U test was used to compare the mean changes in WOMAC and SF-36 scores from baseline at respective time points between groups, whereas Wilcoxon signed-rank test was used to compare the mean changes in WOMAC and SF-36 from baseline to each time points within group. All statistical assessments were tested at the two-tailed significance level of 0.05 using SAS 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Study population

Forty-seven (47) subjects were screened and enrolled in the study. A total of 24 subjects were randomized to the A+HA group and 23 subjects were randomized to the placebo group (Fig. 1). In both treatment groups, the mean age of the subjects was 61.5±9.9 years for the A+HA group and 60.8±10.7 years for the placebo group; and about three-fourths (18/24 vs 17/23) of them were women. No significant difference was found between the two treatment groups with regards to demographic characteristics, brief pain inventory, WOMAC score, and SF-36 score at the baseline (Table 1).

3.2. Efficacy

Over the 8-week study period, the A+HA group showed a gradual improvement in WOMAC index. Significant differences between the A+HA group and the placebo group in WOMAC pain (1.6±1.61 vs 3.3±2.16, P = .01), physical function (4.5±4.25 vs 7.9±6.30, P = .03), and composite (6.8±6.01 vs 12.4±8.52, P = .02) scores were observed at Week 8 (Table 2). As depicted in Fig. 2, significant reductions compared with baseline and significant between-group differences in the WOMAC pain, physical function, and composite scores were observed as early as Week 2 and Week 4 respectively, in the A+HA group. At Week 8, the mean changes from baseline for WOMAC pain (−2.6±1.68 vs 0.1±2.67, P < .001), stiffness (−1.2±1.50 vs 0.3±1.19, P = .007), physical function (−5.8±4.39 vs −0.7±7.77, P = .003), and composite (−9.4±5.82 vs −0.3±17.38, P < .001) scores were significantly greater in the A+HA group than the placebo group.

With regards to the results of SF-36 (Table 3), there were no significant differences between the A+HA group and the placebo group in the sub-scores of all the 8 domains and the total score.
over the 8-week study period, except for SF-36 physical functioning sub-score at Week 8 (25.8 ± 3.46 vs 23.4 ± 3.89, \( P = .02 \)). As depicted in Fig. 3, the \( A + HA \) group achieved significant improvements in physical functioning domain (2.3 ± 2.93, \( P = .003 \)), social functioning domain (0.7 ± 1.33, \( P = .04 \)), and total SF-36 score (4.2 ± 6.98, \( P = .002 \)), while the placebo group had a significant improvement in bodily pain domain (0.9 ± 1.01, \( P = .003 \)) as compared with the baseline at Week 4. At Week 8, significant improvements were seen in the physical functioning (2.7 ± 3.10, \( P = .001 \)) and bodily pain (0.7 ± 1.50, \( P < .05 \)) domains as compared with the baseline in the \( A + HA \) group. There were significant differences between groups in the mean change from baseline for the SF-36 physical functioning domain at both Week 4 (\( P = .01 \)) and Week 8 (\( P = .007 \)).

4. Discussion
In the present study, administration of low molecular weight HA as an oral liquid form demonstrated an apparent efficacy for pain relief and improving physical functioning in knee OA patients with mild knee pain as shown by both the within-group as well as between-group differences in the mean changes from the baseline to the end of the study. Overall, oral liquid low molecular weight HA showed a better effect in knee OA symptoms against QoL improvement for knee OA patients with mild knee pain.

For the symptoms relief in knee OA, the reduction in WOMAC pain and physical function sub-scores were significant at 2 weeks after randomization and persisted until the end of our study. This finding was comparable to the previous studies\(^{[8, 9, 17]}\) where significant changes from the baseline to Week 8 were found in the

| WOMAC scores (mean ± SD) | A+HA n = 24 | Placebo n = 23 | \( P \) value |
|--------------------------|-------------|----------------|-------------|
| **Week 2**               |             |                |             |
| Pain                     | 3.1 ± 2.24  | 3.7 ± 2.48     | .58         |
| Stiffness                | 1.2 ± 1.27  | 1.3 ± 1.25     | .74         |
| Physical function        | 8.2 ± 4.75  | 10.0 ± 6.73    | .52         |
| Total                    | 12.5 ± 7.14 | 15.0 ± 9.55    | .54         |
| **Week 4**               |             |                |             |
| Pain                     | 2.4 ± 1.70  | 2.8 ± 1.46     | .37         |
| Stiffness                | 0.8 ± 0.64  | 0.8 ± 0.71     | .91         |
| Physical function        | 5.9 ± 4.37  | 7.5 ± 5.85     | .43         |
| Total                    | 9.0 ± 6.16  | 11.1 ± 7.50    | .46         |
| **Week 8**               |             |                |             |
| Pain                     | 1.6 ± 1.61  | 3.3 ± 2.16     | .01*        |
| Stiffness                | 0.6 ± 0.90  | 1.2 ± 1.11     | .07         |
| Physical function        | 4.5 ± 4.25  | 7.9 ± 6.30     | .03*        |
| Total                    | 6.8 ± 6.01  | 12.4 ± 8.52    | .02*        |

*SD = standard deviation, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

\( * P < .05 \).

Figure 2. Mean change from baseline in WOMAC. The mean change of (A) total score and the scores of (B) pain, (C) stiffness, and (D) physical function subscales are shown. \( * P \) value < .05 against placebo group and \( * * P \) value < .01 against baseline. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
that the world over, the problem of difficulty of swallowing solid oral dosage forms and offer a better compliance in elderly knee OA patients.

Yet, it is of importance to note that the oral liquid supplement in our study is a combination of low molecular weight HA with molecular weight between $5 \times 10^4$ and $5 \times 10^5$ Da, glucosamine, and chondroitin sulfate. As the supplement contains glucosamine and chondroitin which are usually consumed as chondroprotective agents, the potential effects of ingredients other than HA on knee OA symptom relief cannot be denied. However, the beneficial effects of this oral liquid low molecular HA OA supplement on knee OA patients with mild knee pain symptom were confirmed in this study. Besides the combination used in our study product, another combination (HA, chondroitin sulfate, and chondroitin which are usually consumed as chondroprotective agents) the potential effects of ingredients other than HA on knee OA symptom relief cannot be denied. However, the beneficial effects of this oral liquid low molecular HA OA supplement on knee OA patients with mild knee pain symptom were confirmed in this study. Besides the combination used in our study product, another combination (HA, chondroitin sulfate, and hydrolyzed collagen type II) also demonstrated beneficial effects on knee OA in a clinical study.

This study has several limitations. The study participants were recruited from a single site; thus, selection bias may have been introduced. Statistical bias may have been introduced by the small sample size. Information was lacking about the lifestyle of the study population, but all patients did not change their lifestyle in the study period. At the study period, squatting, kneeling, up and down stairs activities, and heavy duty loading motions of the OA knees were suggested to be decreased as possible as they could. Beside, walking, cycling, and swimming activities were encouraged if they could. The present study’s results were of subjective outcomes; thus, may not be generalized to other populations.

### Table 3

SF-36 scores during the 8-week study period.

| SF-36 scores (mean ± SD) | A+HA n = 24 | Placebo n = 23 | P value |
|--------------------------|-------------|---------------|---------|
| **Week 2**               |             |               |         |
| Physical functioning     | 23.7 ± 3.52 | 23.1 ± 3.37   | .62     |
| Role limitations-physical| 4.9 ± 1.49  | 4.8 ± 1.53    | .99     |
| Bodily pain              | 9.2 ± 1.45  | 9.2 ± 1.43    | .98     |
| General health           | 18.2 ± 3.07 | 17.5 ± 4.59   | .71     |
| Vitality                 | 17.8 ± 2.39 | 18.3 ± 2.10   | .53     |
| Social functioning       | 8.9 ± 1.23  | 8.8 ± 1.62    | .93     |
| Role limitations-emotional| 0.2 ± 0.86 | 0.4 ± 0.96    | .42     |
| Mental health            | 23.1 ± 2.82 | 24.0 ± 2.92   | .45     |
| Total                    | 105.9 ± 11.10| 103.3 ± 15.71| .85     |
| **Week 4**               |             |               |         |
| Physical functioning     | 25.3 ± 2.38 | 22.5 ± 6.23   | .16     |
| Role limitations-physical| 4.8 ± 1.13  | 5.1 ± 1.35    | .58     |
| Bodily pain              | 9.5 ± 1.24  | 9.6 ± 1.22    | .31     |
| General health           | 18.1 ± 3.04 | 18.2 ± 2.54   | .68     |
| Vitality                 | 17.5 ± 3.32 | 18.8 ± 2.01   | .37     |
| Social functioning       | 9.4 ± 0.90  | 9.0 ± 1.56    | .47     |
| Role limitations-emotional| 0.3 ± 0.82 | 0.4 ± 0.92    | .92     |
| Mental health            | 23.7 ± 2.92 | 23.4 ± 3.24   | .74     |
| Total                    | 108.8 ± 10.27| 106.0 ± 12.69| .51     |
| **Week 8**               |             |               |         |
| Physical functioning     | 25.8 ± 3.46 | 23.4 ± 3.89   | .02     |
| Role limitations-physical| 5.0 ± 1.36  | 4.7 ± 1.71    | .20     |
| Bodily pain              | 9.8 ± 1.77  | 8.7 ± 1.76    | .09     |
| General health           | 18.2 ± 2.89 | 17.1 ± 2.98   | .17     |
| Vitality                 | 18.1 ± 3.21 | 17.0 ± 3.53   | .16     |
| Social functioning       | 8.8 ± 1.24  | 8.9 ± 1.35    | .64     |
| Role limitations-emotional| 0.1 ± 0.45 | 0.5 ± 1.15    | .23     |
| Mental health            | 23.4 ± 2.91 | 22.4 ± 4.12   | .51     |
| Total                    | 107.0 ± 13.76| 101.5 ± 12.27| .07     |

SD = standard deviation; SF-36 = 36-item Short-Form Survey.

* P < .05.
Figure 3. Mean change from baseline in SF-36. The mean change of (A) total score and the scores of (B) physical functioning, (C) role limitations due to physical health, (D) bodily pain, (E) general health, (F) vitality, (G) social functioning, (H) role limitations due to emotional problems, and (I) mental health domains are shown. *P value < .05 against placebo group and †P value < .05 against baseline. SF-36 = 36-item Short-Form Survey.
In summary, oral administration of liquid low molecular weight HA appeared to be effective in the alleviation of knee OA patients with mild knee pain symptoms, particularly in pain and functional changes, and the effect is apparent as early as 2 weeks after first administration. Further study to evaluate the long-term effect and radiographic changes of oral liquid low molecular weight HA in knee OA is warranted.

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