Clinical Trial/Experimental Study

Medicine®

OPEN

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

Shyu-Jye Wang, MD[a,b,*], Ya-Hui Wang, MD[c], Liang-Chen Huang, MD[d]

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

Editor: Jenn-Haung Lai.

This study was sponsored by the Top Pharm & Medicalware, Taiwan.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Institute of Medicine, China Medical University, Taichung, [b] Department of Orthopaedics, China Medical University Hospital, Taichung, [c] Department of Ophthalmology, Taipei Municipal Wangfang Hospital, Taipei, [d] Department of General Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan, Republic of China.

[*] Correspondence: Shyu-Jye Wang, No. 2, Yu-Der road, North district, Tai-Chung city 404, Taiwan, Republic of China (e-mail: sjwang1214@yahoo.com.tw).

How to cite this article: Wang SJ, Wang YH, Huang LC. 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. Medicine 2021;100:5(e24252).

Received: 12 July 2020 / Received in final form: 13 December 2020 / Accepted: 17 December 2020

http://dx.doi.org/10.1097/MD.0000000000024252

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[3] as an indication for the treatment of pain in knee OA patients who have failed response adequately to non-pharmacologic therapy, non-steroidal anti-inflammatory drugs or analgesics. Despite its proven efficacy and safety,[4–6] 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.[7]

The efficacy of low molecular weight HA ingestion in knee OA has been investigated in several studies and the results remain controversial.[8–12] For instance, Sato and Iwaso[8] and Kalman et al[9] 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[10] 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, $P < .05$) and visual analogue scale (VAS) pain score (4.06 ± 0.53 vs 5.84 ± 0.50, $P < .05$) 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.[13]

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 20 mL liquid combination supplement containing 50 mg of HA with low molecular weight (5×10^4–5×10^5 Da), 750 mg of glucosamine, and 250 mg of chondroitin. Subjects who fulfilled all the eligibility criteria were randomized to administer either a bottle contained 20 mL of A$^+$HA or a bottle contained 20 mL of placebo daily for 8 weeks. Efficacy assessments were performed at week 2, week 4, and week 8 after randomization.

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[14] 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 ≥40 kg/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 20 mL oral solution containing a mixture of 50 mg HA (5×10^4–5×10^5 Da), 750 mg glucosamine, and 250 mg chondroitin. The placebo was a 20 mL 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.[15] 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)[16] 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 summing all sub-scores of the covered domains.

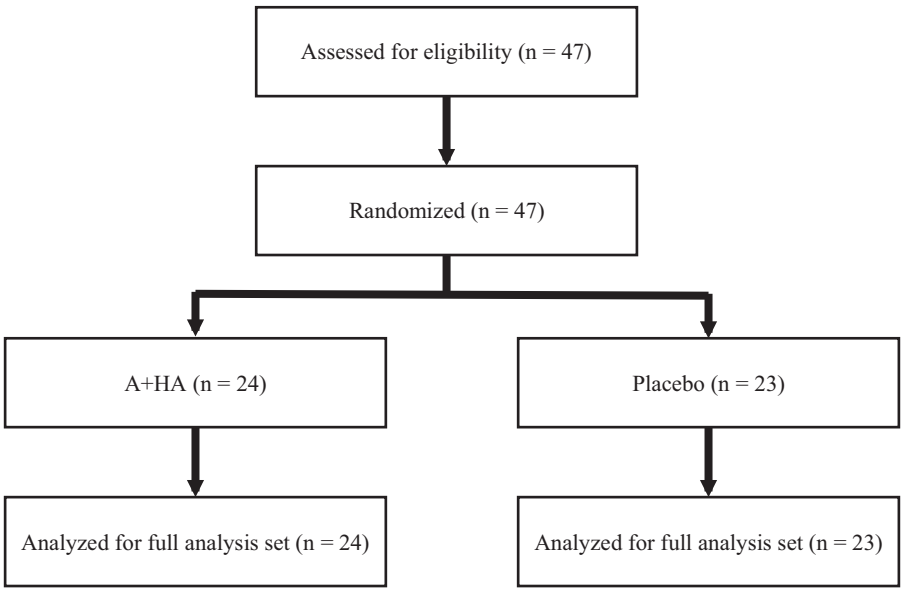

Figure 1. Study flow diagram.

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 2 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 ± 10.38, $P < .001$) 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

Table 1

Baseline demographics and clinical characteristics of all randomized subjects.

	A+HA n = 24	Placebo n = 23	*P* value
Gender (n, %)			.93
Male	6 (25.0%)	6 (26.1%)	
Female	18 (75.0%)	17 (73.9%)	
Age, mean ± SD, y	61.51 ± 9.93	60.8 ± 10.70	.71
Weight, mean ± SD, kg	65.8 ± 9.49	73.4 ± 29.10	.79
Height, mean ± SD, cm	161.6 ± 7.90	152.2 ± 30.1	.53
BMI, mean ± SD, kg/m^2	25.17 ± 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			
Pain	4.3 ± 2.76	4.0 ± 2.91	.58
Stiffness	1.7 ± 1.55	1.2 ± 0.98	.34
Physical function	9.3 ± 5.91	11.5 ± 9.59	.62
Total	15.2 ± 7.79	16.7 ± 12.65	.87
SF-36 scores, mean ± SD			
Physical functioning	23.2 ± 3.19	22.0 ± 5.66	.72
Role limitations-physical	5.3 ± 1.59	5.0 ± 1.83	.65
Bodily pain	8.9 ± 1.73	8.6 ± 1.51	.30
General health	17.7 ± 3.29	18.1 ± 2.46	.88
Vitality	17.4 ± 3.85	17.5 ± 3.08	.85
Social functioning	8.6 ± 1.58	8.5 ± 1.62	.83
Role limitations-emotional	0.2 ± 0.66	0.7 ± 1.18	.12
Mental health	22.3 ± 3.56	22.6 ± 2.68	.97
Total	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.

Table 2

WOMAC scores during the 8-week study period.

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.
* $P < .05$.

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

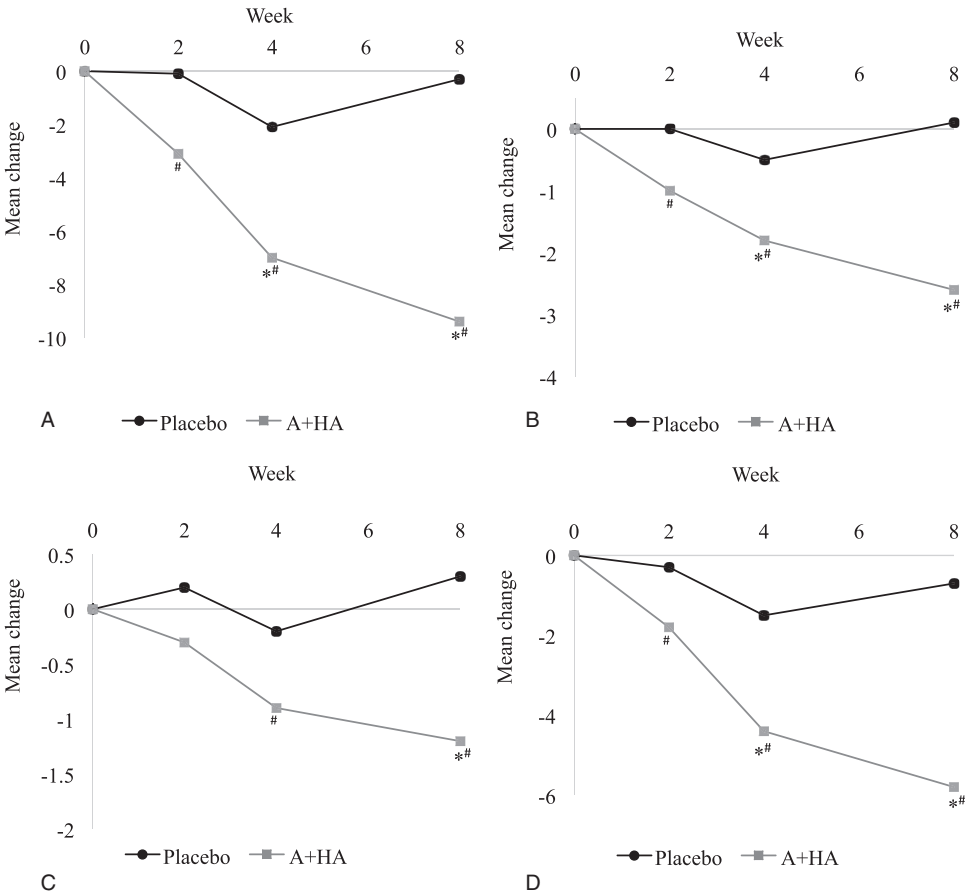

Figure 2. Mean change from baseline in WOMAC. The mean change of (A) total score and the scores of (B) pain, (C) stiffness, and (D) physical function subscales are shown. *P value < .05 against placebo group and #P value < .01 against baseline. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

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 ± 0.68	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 ± 2.98	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	18.6 ± 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 ± 1.38	4.7 ± 1.71	.20
Bodily pain	9.8 ± 1.77	8.7 ± 1.78	.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.
* $P < .05$.

WOMAC pain, physical function, and total scores in the oral HA treatment group. However, significant differences in WOMAC scores from baseline to Week 8 were also observed in the placebo group in the 2 above mentioned studies.[8,9]

With regard to the QoL, the oral HA treatment group showed a significant improvement in the SF-36 physical functioning domain but not in the role limitations due to physical health domain at Week 8, which is in contrast to the results found by Kalman et al.[9] Also, in line with the results of HA injection,[18] we found that HA ingestion did not improve much in the mental health dimension in SF-36 (vitality, social functioning, role limitations due to emotional problem, and emotional well-being domains) and only modest but significant improvement was observed in the SF-36 physical functioning domain at the end of our study. Nonetheless, HA ingestion offers an advantage over HA injection in avoiding potential complications at the injection site and discomfort associated with repeated injections.[19]

Furthermore, difficulty swallowing is a common problem in elderly patients and swallowing pills, tablets, or capsules has been a challenge to them.[20–22] It may cause poor compliance[23] and administration errors[24] thereby compromise the efficacy of a treatment. To date, most of the HA oral supplements being studied are available as tablet or capsule forms.[8–13] Concerning that the world's population is aging and the incidence of knee OA increases by age, this oral liquid formulation of HA may overcome 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 5×10^4 and 5×10^5 Da, glucosamine, and chondroitin sulfate. As the supplement contains glucosamine and chondroitin which are usually consumed as chondroprotective agents,[25] 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, hydrolyzed collagen type II, and hydrolyzed keratin) also demonstrated beneficial effects on knee OA in a clinical study.[26]

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, kneeing, 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.

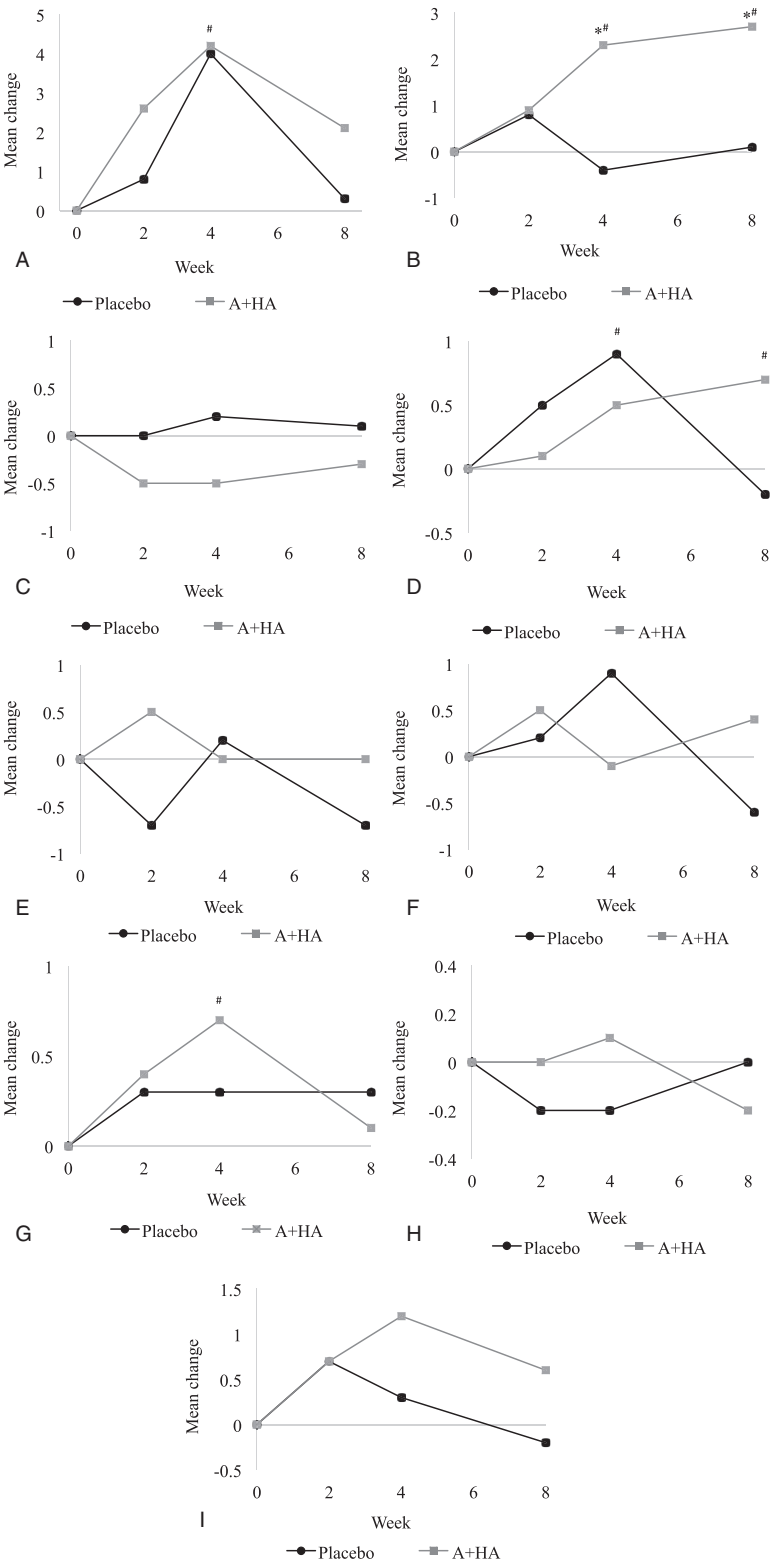

Figure 3. Mean change from baseline in SF-36. The mean change of (A) total score and the scores of (B) physical functioning, (C) role limitations due to physical health, (D) bodily pain, (E) general health, (F) vitality, (G) social functioning, (H) role limitations due to emotional problems, and (I) 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 physical functions, 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.

Acknowledgments

The authors thank all the participants and study staffs of the study.

Author contributions

Conceptualization: Shyu-Jye Wang.
Formal analysis: Shyu-Jye Wang, Ya-Hui Wang, Liang-Chen Huang.
Investigation: Shyu-Jye Wang.
Resources: Ya-Hui Wang, Liang-Chen Huang.
Validation: Ya-Hui Wang, Liang-Chen Huang.
Writing – original draft: Shyu-Jye Wang.
Writing – review & editing: Shyu-Jye Wang, Ya-Hui Wang, Liang-Chen Huang.

References

[1] Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73:1323–30.
[2] Tamer TM. Hyaluronan and synovial joint: function, distribution and healing. Interdiscip Toxicol 2013;6:111–25.
[3] Aggarwal A, Sempowski IP. Hyaluronic acid injections for knee osteoarthritis. Systematic review of the literature. Can Fam Physician 2004;50:249–56.
[4] Migliore A, Procopio S. Effectiveness and utility of hyaluronic acid in osteoarthritis. Clin Cases Miner Bone Metab 2015;12:31–3.
[5] Miller LE, Block JE. US-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. Clin Med Insights Arthritis Musculoskelet Disord 2013;6:57–63.
[6] Maheu E, Rannou F, Reginster JY. Efficacy and safety of hyaluronic acid in the management of osteoarthritis: evidence from real-life setting trials and surveys. Semin Arthritis Rheum 2016;45:S28–33.
[7] Oe M, Tashiro T, Yoshida H, et al. Oral hyaluronan relieves knee pain: a review. Nutr J 2016;15:11.
[8] Sato T, Iwaso H. An effectiveness study of hyaluronic acid [Hyabest®(J)] in the treatment of osteoarthritis of the knee on the patients in the United States. J New Rem Clin 2009;58:249–56.
[9] Kalman DS, Heimer M, Valdeon A, et al. Effect of a natural extract of chicken combs with a high content of hyaluronic acid (Hyal-Joint®) on pain relief and quality of life in subjects with knee osteoarthritis: a pilot randomized double-blind placebo-controlled trial. Nutr J 2008;7:3.
[10] Nelson FR, Zvirbulis RA, Zonca B, et al. The effects of an oral preparation containing hyaluronic acid (Oralvisc(R)) on obese knee osteoarthritis patients determined by pain, function, bradykinin, leptin, inflammatory cytokines, and heavy water analyses. Rheumatol Int 2015;35:43–52.
[11] Tashiro T, Seino S, Sato T, et al. Oral administration of polymer hyaluronic acid alleviates symptoms of knee osteoarthritis: a double-blind, placebo-controlled study over a 12-Month period. Scientific-WorldJournal 2012;2012:167928.
[12] Jensen GS, Attridge VL, Lenninger MR, et al. Oral intake of a liquid high-molecular-weight hyaluronan associated with relief of chronic pain and reduced use of pain medication: results of a randomized, placebo-controlled double-blind pilot study. J Med Food 2015;18:95–101.
[13] Ricci M, Micheloni GM, Berti M, et al. Clinical comparison of oral administration and viscosupplementation of hyaluronic acid (HA) in early knee osteoarthritis. Musculoskelet Surg 2017;101:45–9.
[14] Ahlback S. Osteoarthrosis of the knee. A radiographic investigation. Acta Radiol Diagn (Stockh) 1968;(suppl):7–2.
[15] Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
[16] Lu J-FR, Tseng H-M, Tsai Y-J. Assessment of health-related quality of life in Taiwan (I): development and psychometric testing of SF-36 Taiwan version. Taiwan J Public Health 2003;22:501–11.
[17] Cicero AFG, Girolimetto N, Bentivenga C, et al. Short-term effect of a new oral sodium hyaluronate formulation on knee osteoarthritis: a double-blind, randomized, placebo-controlled clinical trial. Diseases 2020;8:26.
[18] Farr Ii J, Miller LE, Block JE. Quality of life in patients with knee osteoarthritis: a commentary on nonsurgical and surgical treatments. Open Orthop J 2013;7:619–23.
[19] Adams ME, Lussier AJ, Peyron JG. A risk-benefit assessment of injections of hyaluronan and its derivatives in the treatment of osteoarthritis of the knee. Drug Saf 2000;23:115–30.
[20] Wright D. Medication administration in nursing homes. Nurs Standard 2002;16:33–8.
[21] Schiele JT, Quinzler R, Klimm HD, et al. Difficulties swallowing solid oral dosage forms in a general practice population: prevalence, causes, and relationship to dosage forms. Eur J Clin Pharmacol 2013;69:937–48.
[22] Stegemann S, Gosch M, Breitkreutz J. Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy. Int J Pharm 2012;430:197–206.
[23] Fusco S, Cariati D, Schepisi R, et al. Management of oral drug therapy in elderly patients with dysphagia. J Gerontol Geriatr 2016;64:9–20.
[24] Kelly J, Wright D, Wood J. Medicine administration errors in patients with dysphagia in secondary care: a multi-centre observational study. J Adv Nurs 2011;67:2615–27.
[25] Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006;354:795–808.
[26] Oliviero F, Ramonda R, Hoxha A, et al. Effect of an oral preparation containing hyaluronic acid, chondroitin sulfate, hydrolyzed collagen type II and hydrolyzed keratin on synovial fluid features and clinical indices in knee osteoarthritis. A pilot study. Reumatismo 2020;72:125–30.