Comparison of Single Intra-Articular Injection of Novel Hyaluronan (HYA-JOINT Plus) with Synvisc-One for Knee Osteoarthritis

A Randomized, Controlled, Double-Blind Trial of Efficacy and Safety

Shu-Fen Sun, MD, Chien-Wei Hsu, MD, Huey-Shyan Lin, PhD, I-Hsiu Liou, MD, Yin-Han Chen, MD, and Chia-Ling Hung, MD

Investigation performed at the Kaohsiung Veterans General Hospital, Kaohsiung City, Taiwan

Background: Viscosupplementation has been widely used for the treatment of knee osteoarthritis. Because we found no well-controlled trial comparing single-injection regimens of hyaluronan for knee osteoarthritis, we compared the efficacy and safety of a single intra-articular injection of a novel cross-linked hyaluronan (HYA-JOINT Plus) with a single injection of Synvisc-One in patients with knee osteoarthritis.

Methods: In a prospective, randomized, controlled, double-blind trial with a 6-month follow-up, 132 patients with knee osteoarthritis (Kellgren-Lawrence grade 2 or 3) were randomized to receive 1 intra-articular injection of 3 mL of HYA-JOINT Plus (20 mg/mL) (n = 66) or 6 mL of Synvisc-One (8 mg/mL) (n = 66). The primary outcome was the change from baseline in the visual analog scale (VAS) (0 to 100 mm) pain score at 6 months. Secondary outcome measures included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, Likert scale), Lequesne index, timed "Up & Go" (TUG) test, single-limb stance (SLS) test, use of rescue analgesics, and patient satisfaction.

Results: A total of 121 patients were available for the intention-to-treat analysis at 6 months. Both groups had a significant improvement in the VAS, WOMAC, and Lequesne index scores at each follow-up visit ($p < 0.001$). Patients who received HYA-JOINT Plus experienced a significantly greater improvement in the VAS pain score at 1, 3, and 6 months compared with those treated with Synvisc-One (adjusted mean difference: −12.0, −8.5, and −6.6; $p = 0.001$, 0.033, and 0.045, respectively). There were no significant between-group differences in any of the secondary outcomes except the WOMAC stiffness scores at 6 months, which favored HYA-JOINT Plus treatment ($p = 0.043$). The TUG time did not change significantly in either group during the study ($p > 0.05$), but the SLS time improved significantly in both the HYA-JOINT Plus and the Synvisc-One group ($p = 0.004$ and $p = 0.022$, respectively). No significant between-group differences were observed with respect to patient satisfaction or consumption of analgesics. No serious adverse events occurred following the injections.

Conclusions: A single injection of either HYA-JOINT Plus or Synvisc-One is safe and effective for 6 months in patients with knee osteoarthritis. HYA-JOINT Plus is superior to Synvisc-One in terms of reducing the VAS pain score at 1, 3, and 6 months and the WOMAC stiffness score at 6 months, with similar safety.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

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Viscosupplementation with hyaluronan is a well-established treatment option for knee osteoarthritis. The goal of viscosupplementation is to reduce pain and improve viscoelasticity of synovial fluid[1,2]. Hyaluronan may provide biological actions, including anti-inflammatory, antinociceptive, and anabolic effects[3-6]. Moreover, it has been known to

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stimulate endogenous hyaluronan synthesis through CD44 receptor binding[4]. Conflicting conclusions regarding the efficacy of hyaluronan for knee osteoarthritis have been reported[7-11]. The majority of studies have suggested small-to-strong effects, while a minority have shown no benefit when compared with placebos. Despite controversies, hyaluronan injections are recommended in the professional guidelines for patients who cannot be effectively managed with nonpharmacologic treatment and simple analgesics[12].

There are several hyaluronan formulations that differ in their origin, concentration, and dosing regimens. Most initial hyaluronan preparations were derived from rooster-comb tissue and required 3, 4, or 5 intra-articular injections. Subsequent, newer hyaluronan products were engineered to provide durable activity and require fewer injections. For example, both HYA-JOINT Plus (SciVision Biotech) and Synvisc-One (hylan G-F 20; Sanofi-aventis) consist of chemically cross-linked hyaluronan, resulting in increased viscoelasticity, and require only 1 injection. The single-injection regimen is attractive, as it may decrease patient time expenditure and discomfort associated with the injection process and offer potential safety benefits[13].

Synvisc-One is composed of 6 mL of 0.8% avian-derived hyaluronan (8 mg/mL) that underwent formaldehyde modification and a divinyl sulfone cross-linking process. In contrast, HYA-JOINT Plus, the focus of this study, is produced by microbial fermentation. HYA-JOINT Plus is synthesized by a novel cross-linking process by 1,4-butanediol diglycidyl ether (BDDE) to create an anti-degradation feature (see Appendix). The carefully controlled cross-linking creates a viscous gel with increased density of hyaluronan (2% of hyaluronan, 20 mg/mL). We are not aware of any well-controlled, high-quality study comparing single-injection regimens of hyaluronan for knee osteoarthritis. The purpose of this study was to compare the efficacy and safety of a single intra-articular injection of the novel cross-linked hyaluronan HYA-JOINT Plus with a single injection of Synvisc-One in patients with knee osteoarthritis.

TABLE I Demographic and Baseline Characteristics of Intention-to-Treat Population

	HYA-JOINT Plus (N = 62)	Synvisc-One (N = 59)	P Value
Sex*			0.432
Male	14 (23%)	17 (29%)	
Female	48 (77%)	42 (71%)	
Radiographic Kellgren-Lawrence grade*			0.855
2	40 (65%)	39 (66%)	
3	22 (36%)	20 (34%)	
Osteoarthritis site*			0.078
Left	29 (47%)	37 (63%)	
Right	33 (53%)	22 (37%)	
Age† *(yr)*	62.7 ± 8.4	62.5 ± 10.0	0.890
Body mass index† *(kg/m²)*	24.7 ± 3.3	25.2 ± 4.2	0.457
Osteoarthritis duration† *(yr)*	5.4 ± 4.4	5.2 ± 4.6	0.832
≤5 yr*	40 (65%)	36 (61%)	0.293
>5 to ≤10 yr*	15 (24%)	20 (34%)	
>10 yr*	7 (11%)	3 (5%)	
VAS score† *(mm)*	59.4 ± 15.8	55.7 ± 16.4	0.212
WOMAC score† *(points)*			
Pain (0-20)	9.9 ± 3.4	9.8 ± 3.3	0.968
Stiffness (0-8)	3.2 ± 1.8	3.2 ± 1.8	0.826
Function (0-68)	34.7 ± 13.5	35.8 ± 13.9	0.649
Total (0-96)	47.8 ± 17.7	48.8 ± 17.3	0.744
Lequesne index† *(points)*	11.1 ± 4.7	10.4 ± 4.0	0.359
TUG time† *(sec)*	12.3 ± 8.7	12.6 ± 13.3	0.902
SLS time† .*(sec)*	17.4 ± 20.9	15.8 ± 18.2	0.652

*The values are given as the number of patients with the percentage in parentheses. †The values are given as the mean and the standard deviation.

Materials and Methods

Study Design and Participants (Table I)

This was a prospective, randomized, controlled, double-blind (patient and observer blinded) study with 6 months of follow-up done between September 2014 and August 2015. Subjects were recruited through advertisements placed in a rehabilitation department of a university-affiliated tertiary-care medical center. The inclusion and exclusion criteria are shown in Table II. All subjects gave written informed consent before participating in the study. The study was approved by the institutional review board for human investigation and was registered at ClinicalTrials.gov (NCT02686047).

The study consisted of a screening visit; a baseline visit during which the intra-articular injection was performed; and follow-up visits at 1, 3, and 6 months post-injection. Patients seen for screening returned for the baseline visit (if they had been chosen for the study) after a 1-week period to allow washout of nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics. Before randomization, demographic data and baseline assessments were collected.

At 1 week post-injection, we contacted participants via telephone to collect data regarding the safety of the injection.

Randomization Procedures

Enrolled patients were randomized (1:1) to 2 groups. To do this, sequentially numbered opaque envelopes in which the allocation was sealed were generated by a person who was not clinically involved in the study. When a patient consented to the trial, he or she selected 1 of the envelopes and then was given the allocated hyaluronan.

Intervention

The patients in the HYA-JOINT Plus group received a single 3-mL intra-articular injection of HYA-JOINT Plus. The Synvisc-One group received 1 injection of 6 mL of Synvisc-One. All of the injections were done by the same experienced physician using aseptic procedures without ultrasound or other imaging guidance.

TABLE II Inclusion and Exclusion Criteria

Inclusion criteria
Age of 40-85 years
Symptomatic knee osteoarthritis for ≥6 months despite nonoperative treatment such as analgesics, NSAIDs, and/or physical therapy
Average knee pain score of ≥30 mm on 100-mm VAS
Kellgren-Lawrence grade-2 or 3 knee osteoarthritis seen on radiographs made within previous 6 months
Radiographic evidence of bilateral knee osteoarthritis not reason for exclusion if global VAS pain score in contralateral knee <30 mm
Exclusion criteria
Previous orthopaedic surgery on spine or lower limb
Disabling osteoarthritis of either hip or foot
Knee instability, apparent joint effusion, or marked valgus/varus deformity
Known allergy to avian proteins or hyaluronan products
Confirmed or suspected pregnancy, or lactating
Intra-articular injections into knee in previous 6 months
Any specific medical conditions (rheumatoid arthritis, active infection, hemiparesis, neoplasm, etc.) that would interfere with assessments

The investigator who performed all of the assessments was blinded to the randomization and treatment. The patients were also blinded, by preventing visual access to the injection field with a screen placed between them and their knee during the injection process. They also were not informed of which hyaluronan they had received during the study period.

No regular analgesics, glucosamine or chondroitin, NSAIDs, or physical therapy for the knee were permitted during the study. Acetaminophen (500 mg; maximum daily dose, 4 g) was the only rescue medication allowed for knee pain. Acetaminophen was not permitted during the 24-hour period prior to each study visit. Use of rescue medication during the study period was recorded by the patient in a diary.

Major protocol violations included surgery, initiation of physical therapy, and use of proscribed medications. Patients were considered to be noncompliant when they missed any visit.

Outcome Measures

The primary outcome was the change, between baseline and 6 months, in the pain score as marked on a 0 to 100-mm visual analog scale (VAS; 0 = no pain and 100 = worst possible pain)[14]. When marking the VAS, the patient was asked to rate the average severity of the knee pain on knee movement over the previous week.

Secondary outcome measures included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, Likert scale), Lequesne index, timed "Up & Go" (TUG) test, single-limb stance (SLS) test, use of rescue analgesics, and patient satisfaction (see Appendix)[15-19].

Safety Assessment

The safety assessment was based on adverse events reported by the patients and physical findings by the evaluator at each follow-up visit. It was left to the judgment of the evaluator to decide whether each adverse event was related to the study treatment or not. A serious adverse event was defined as an event that was fatal, life-threatening, permanently disabling, or requiring hospitalization.

Statistical Analysis

With use of SPSS SamplePower 3.0 software (IBM) and the statistical method employed for the study purpose, independent-samples 1-way analysis of covariance (ANCOVA) using baseline data for the outcome variable as the covariate, the required sample size was estimated to be 59 participants per group (power = 0.8, alpha = 0.05; since no preliminary data were available, we used a medium-level Cohen effect size of 0.09 for the R^2 for the covariate and a medium-level effect size of 0.25 for ANOVA [analysis of variance]). Assuming a 10% dropout rate, the number of participants was increased to 65 per group.

Outcomes were assessed in an intention-to-treat analysis. The intention-to-treat population comprised all patients who had received the injection and had undergone at least 1 post-baseline assessment; the last-observation-carried-forward method was used to account for missing data.

All statistical procedures were conducted with SPSS software (version 12.0). Baseline characteristics were compared using t tests and chi-square tests. Independent-samples 1-way ANCOVA using baseline data for outcome variables as the covariates were utilized to analyze differences between the 2 groups with regard to their primary and secondary outcomes at 1, 3, and 6 months post-injection. Johnson-Neyman analysis was used to find the region of significant difference between groups when the assumption of equal within-group regression coefficients of ANCOVA was violated. Changes in primary and secondary outcome measures among baseline, 1, 3, and 6-month follow-up evaluations were assessed using repeated-measures 1-way ANOVA and the Bonferroni post hoc test. P values of <0.05 were regarded as significant.

Results

Patient Characteristics

A total of 153 participants were assessed for eligibility, and 132 of them were randomized to either the HYA-JOINT Plus group (n = 66) or the Synvisc-One group (n = 66) (Fig. 1).

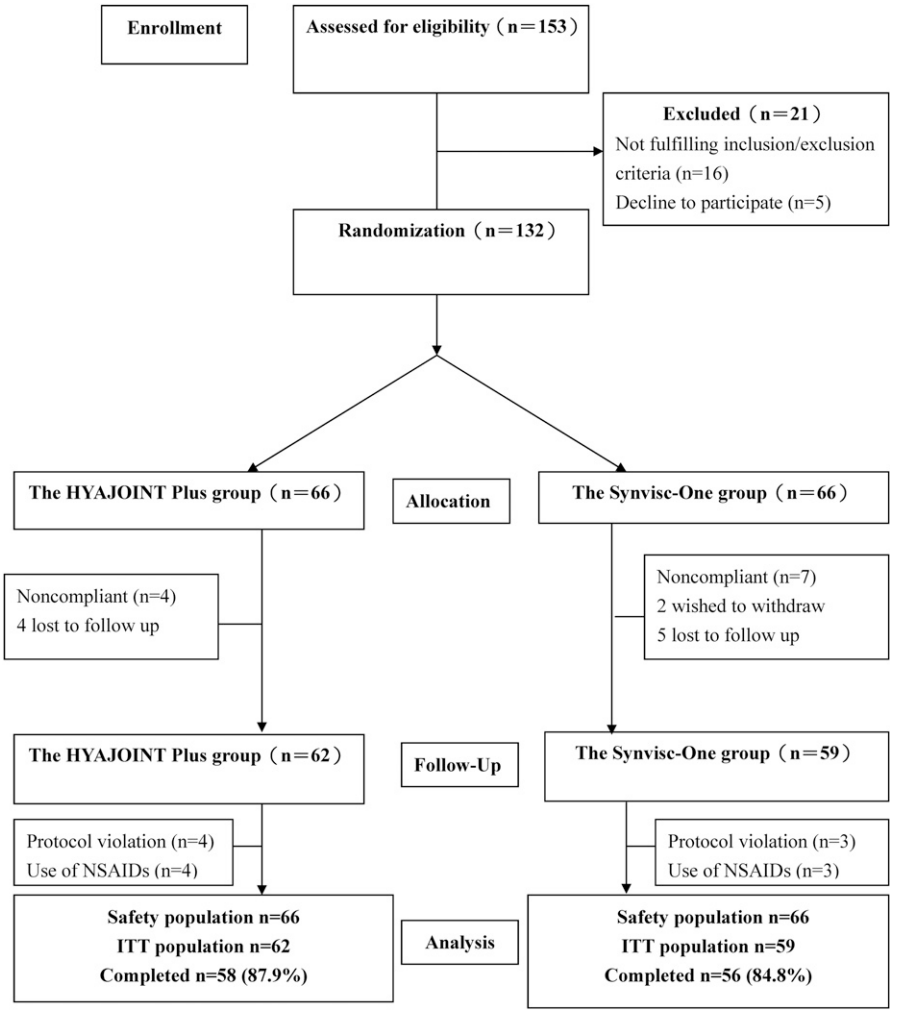

Fig. 1

Flow of participants through the trial. ITT = intention-to-treat.

Eleven patients did not return for follow-up visits during the study period, leaving 121 patients available for the intention-to-treat analysis at the 6-month follow-up evaluation. We were able to contact all 11 patients by telephone at the time of the missed follow-up visits, and none of the 132 patients reported an adverse event. There were no significant differences between the HYA-JOINT Plus and Synvisc-One groups with regard to demographic or baseline data ($p > 0.05$) (Table I). The patients were predominantly female (74.4%), and the mean age was approximately 63 years.

Primary and Secondary Outcomes

Both groups showed significant improvements in the VAS pain score, WOMAC score (including the 3 subscale scores), and Lequesne index score among the baseline, 1, 3, and 6-month visits ($p < 0.001$) (Table III).

Compared with baseline, the mean VAS scores improved by 34.2, 34.6, and 33.3 mm at the 1, 3, and 6-month follow-up evaluations in the HYA-JOINT Plus group, whereas they improved by 19.9, 22.8, and 23.4 mm, respectively, in the Synvisc-One group (Table III). Using ANCOVA with baseline data as a covariate showed that the patients who had received HYA-JOINT Plus had significantly greater improvements in the mean VAS pain score than the patients who had received Synvisc-One (adjusted mean difference between groups, −12.0, −8.5, and −6.6 [$p = 0.001$, $p = 0.033$, and $p = 0.045$] at 1, 3, and 6 months, respectively) (Table III). The maximal between-group difference in the VAS pain score was at 1 month, with an adjusted mean difference of −12.0 ($p = 0.001$).

There was no significant between-group difference, at any follow-up time point, in the Lequesne index score, the total WOMAC score, or any of the 3 WOMAC subscale scores except stiffness, which showed a small but significant difference favoring the HYA-JOINT Plus group at 6 months ($p = 0.043$) (Table III).

Within-group comparison of the TUG times did not show a significant change in either group during the study period ($p > 0.05$), but the SLS time improved significantly in both groups ($p = 0.004$ and $p = 0.022$) (Table IV). Because the

TABLE III Comparison of VAS, WOMAC, and Lequesne Index Scores Between Groups

	HYA-JOINT Plus*	Synvisc-One*	Adjusted Mean Difference (95% Confidence Interval)	P Value†
VAS score *(mm)*				
Baseline	59.3 ± 15.8	55.7 ± 16.4		0.212
1 mo	25.1 ± 18.4	35.8 ± 22.1	−12.0 (−19.1, −5.0)	0.001†
3 mo	24.7 ± 19.0	32.9 ± 24.0	−8.5 (−16.4, −0.7)	0.033†
6 mo	26.0 ± 15.6	32.3 ± 19.6	−6.6 (−13.0, −0.2)	0.045†
P value§	<0.001†	<0.001†		
WOMAC pain score *(points)*				
Baseline	9.9 ± 3.4	9.8 ± 3.3		0.968
1 mo	6.4 ± 4.0	6.5 ± 3.7	−0.1 (−1.5, 1.2)	0.855
3 mo	5.8 ± 2.7	5.9 ± 2.8	−0.5 (−1.0, 0.9)	0.927
6 mo	5.7 ± 2.7	6.3 ± 3.1	−0.6 (−1.6, 0.4)	0.236
P value§	<0.001†	<0.001†		
WOMAC stiffness score *(points)*				
Baseline	3.2 ± 1.8	3.2 ± 1.8		0.826
1 mo	1.9 ± 1.7	2.2 ± 1.8	−0.3 (−0.9, 0.3)	0.293
3 mo	2.0 ± 1.5	2.0 ± 1.5	−0.0 (−0.6, 0.5)	0.962
6 mo	1.7 ± 1.2	2.3 ± 1.7	−0.5 (−1.1, 0.0)	0.043†
P value§	<0.001†	<0.001†		
WOMAC function score *(points)*				
Baseline	34.7 ± 13.5	35.8 ± 13.9		0.649
1 mo	26.7 ± 13.2	28.4 ± 13.9	−1.2 (−5.6, 3.3)	0.604
3 mo	25.1 ± 10.7	26.6 ± 12.0	−1.0 (−4.6, 2.6)	0.575
6 mo	24.7 ± 10.1	26.9 ± 12.3	−1.8 (−5.6, 1.9)	0.335
P value§	<0.001†	<0.001†		
WOMAC total score *(points)*				
Baseline	47.8 ± 17.7	48.8 ± 17.3		0.744
1 mo	35.0 ± 17.8	37.1 ± 18.5	−1.7 (−7.8, 4.4)	0.590
3 mo	33.0 ± 13.8	34.5 ± 15.2	−1.2 (−5.9, 3.6)	0.632
6 mo	32.2 ± 13.2	35.5 ± 16.0	−3.0 (−8.0, 2.0)	0.231
P value§	<0.001†	<0.001†		
Lequesne index *(points)*				
Baseline	11.1 ± 4.7	10.4 ± 4.1		0.359
1 mo	7.9 ± 4.8	8.2 ± 4.9	−0.7 (−2.2, 0.8)	0.353
3 mo	7.5 ± 4.0	8.0 ± 4.5	−0.9 (−2.2, 0.4)	0.186
6 mo	7.3 ± 4.3	7.6 ± 4.4	−0.5 (−2.0, 0.9)	0.469
P value§	<0.001†	<0.001†		

*The values are given as the mean and standard deviation. †Between-group difference determined using independent-samples 1-way ANCOVA. ‡A significant difference ($p < 0.05$). §Within-group difference determined using repeated-measures 1-way ANOVA.

assumption of equal within-group regression coefficients of ANCOVA was violated, Johnson-Neyman analyses were performed, and they revealed the region of significant between-group differences in the TUG and SLS times at a particular time point (Table IV, Figs. 2 and 3). Analysis of patients with a baseline TUG time of >18.8 seconds showed that those treated with HYA-JOINT Plus tended to have a better TUG time at 3 months than those treated with Synvisc-One (Table IV, Fig. 2). Analysis of patients with a baseline SLS time of <5.1 seconds demonstrated that those treated with HYA-JOINT Plus tended to have a better SLS time at 1 month than those treated with Synvisc-One, whereas the analysis focusing on patients with a baseline SLS time of >72.6 seconds showed that the 1-month SLS time tended to be better for those treated with Synvisc-One than those treated with HYA-JOINT Plus (Table IV, Fig. 3 upper

TABLE IV Comparison of TUG and SLS Times Between Groups

	HYA-JOINT Plus*	Synvisc-One*	P Value†
TUG time *(sec)*			
Baseline	12.3 ± 8.7	12.6 ± 13.3	0.902
1 mo	11.2 ± 6.1	10.4 ± 3.9	0.925
3 mo	10.9 ± 4.3	10.4 ± 3.7	HYA-JOINT Plus superior when baseline >18.8 sec
6 mo	11.1 ± 5.0	11.4 ± 5.6	0.145
P value‡	0.078	0.23	
SLS time *(sec)*			
Baseline	17.4 ± 20.9	15.8 ± 18.2	0.652
1 mo	23.8 ± 20.7	20.1 ± 20.4	HYA-JOINT Plus superior when baseline <5.1 sec; Synvisc-One superior when baseline >72.6 sec
3 mo	25.4 ± 21.8	19.8 ± 21.2	HYA-JOINT Plus superior when baseline <12.4 sec; Synvisc-One superior when baseline >63.3 sec
6 mo	27.0 ± 21.8	22.0 ± 21.2	0.216
P value‡	0.004§	0.022§	

*The values are given as the mean and standard deviation. †Between-group difference determined using independent-samples 1-way ANCOVA or Johnson-Neyman analyses. ‡Within-group difference determined using repeated-measures 1-way ANOVA. §A significant difference ($p < 0.05$).

graph). Similar findings were noted at the 3-month follow-up evaluation (Fig. 3 lower graph).

Throughout the study, there were no significant differences in acetaminophen consumption between the groups ($p > 0.05$). In the HYA-JOINT Plus group, the acetaminophen consumption decreased from a mean (and standard deviation) of 15.8 ± 6.2 tablets weekly at baseline to 6.4 ± 2.5, 7.8 ± 2.2, and 9.3 ± 2.4 tablets weekly at the 1, 3, and 6-month follow-up evaluations compared with a decrease from 14.9 ± 6.8 tablets weekly at baseline to 7.9 ± 3.7, 8.2 ± 2.5, and 9.9 ± 2.6 tablets weekly at the follow-up evaluations in the Synvisc-One group.

There were no significant between-group differences in patient satisfaction (Table V). The satisfaction was highest at 3 months in both groups.

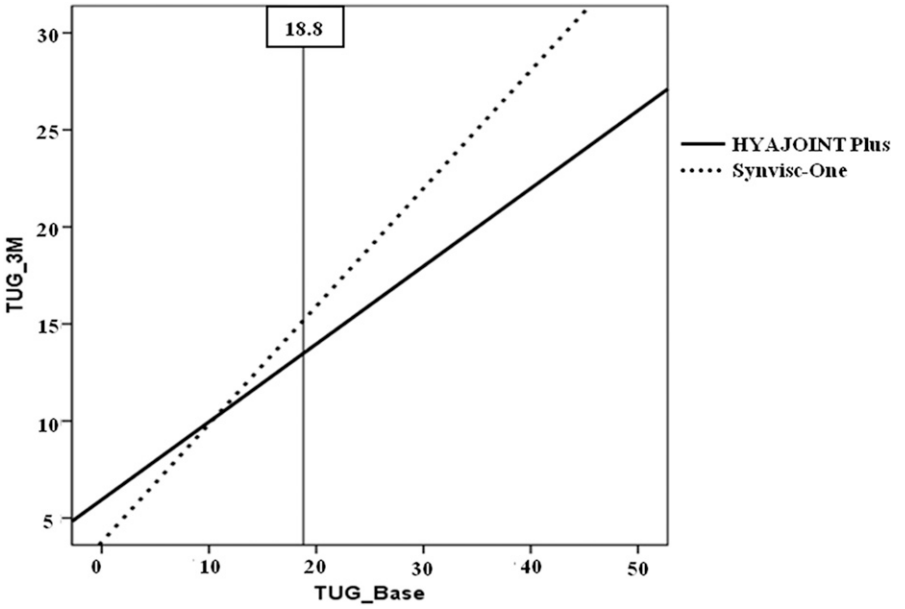

Fig. 2

Graph showing that, of the patients with a baseline TUG time of >18.8 seconds, those treated with HYA-JOINT Plus had a significantly greater improvement in their TUG time at 3 months than those treated with Synvisc-One. The numbers on both axes of the graph indicate the TUG time in seconds.

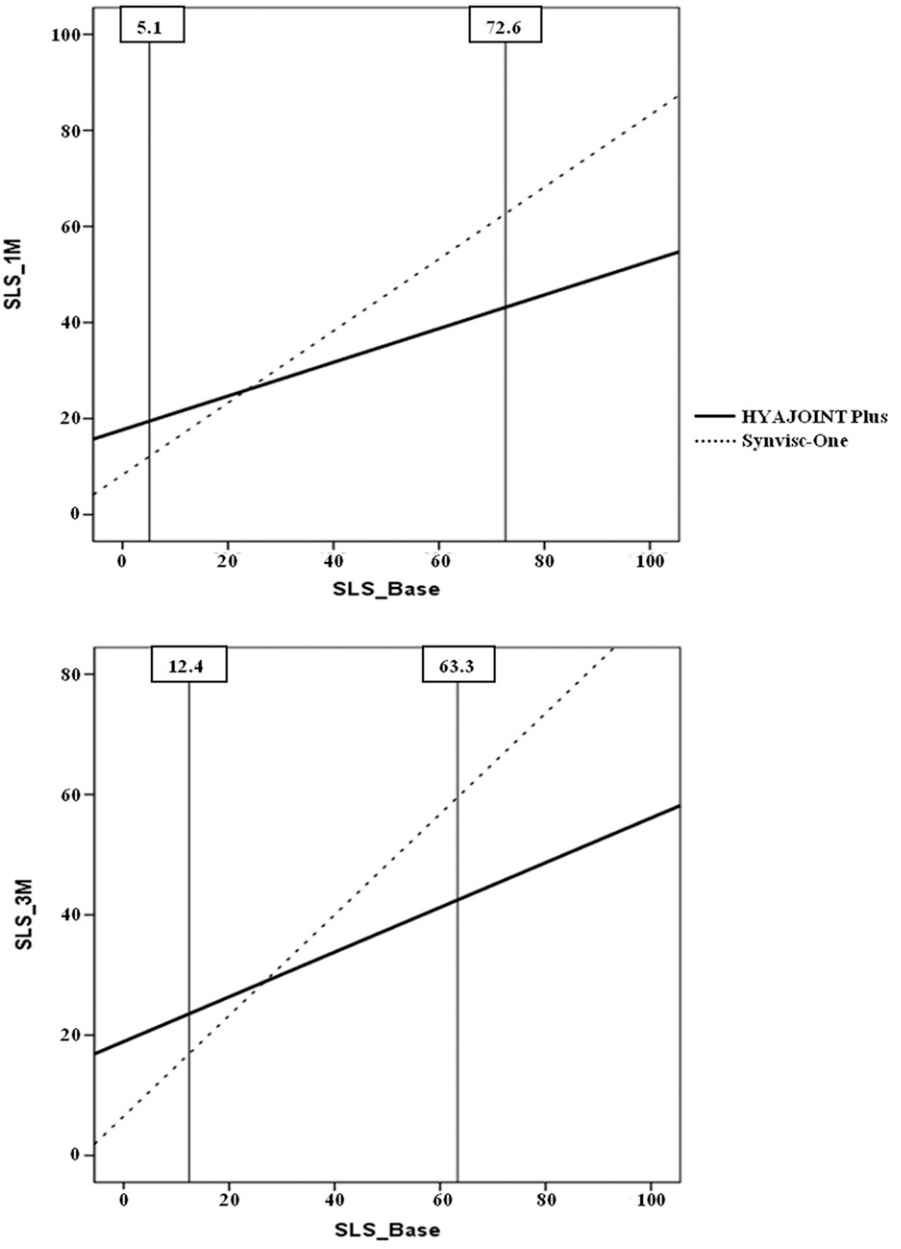

Fig. 3

The upper graph shows that, of the patients with a baseline SLS time of <5.1 seconds, those treated with HYA-JOINT Plus had a significantly greater improvement in their SLS time at 1 month than those treated with Synvisc-One whereas, for the patients with a baseline SLS of >72.6 seconds, treatment with Synvisc-One was superior to HYA-JOINT Plus with regard to the SLS time at 1 month. Similarly, the lower graph shows that, of the patients with a baseline SLS time of <12.4 seconds, those treated with HYA-JOINT Plus had a significantly greater improvement in their SLS time at 3 months than those treated with Synvisc-One whereas, for the patients with a baseline SLS time of >63.3 seconds, treatment with Synvisc-One was superior to HYA-JOINT Plus with regard to the SLS time at 3 months. The numbers on both axes of the graph indicate the SLS time in seconds.

Safety Outcomes

The safety-analysis population comprised all 132 patients who had received an injection of hyaluronan. The frequencies and types of adverse events were comparable between the 2 groups (Table VI). The majority of adverse events were mild or moderate, lasted 1 to 3 days, and resolved spontaneously or responded well to simple analgesics. Twelve patients (9 treated with Synvisc-One and 3 treated with HYA-JOINT Plus) developed joint effusion within 1 week after the injection. It usually resolved spontaneously, but 2 patients in the Synvisc-One group needed arthrocentesis for pain relief. No allergic reactions, pseudosepsis, or serious adverse events occurred during the study. Adverse events did not lead to study discontinuation in either group.

TABLE V Comparison of Patient Satisfaction Between Groups

	HYA-JOINT Plus*	Synvisc-One*	Adjusted Mean Difference (95% Confidence Interval)	P Value†
VAS satisfaction score† *(mm)*				
1 mo	68.6 ± 21.0	66.8 ± 23.6	1.8 (−6.2, 9.8)	0.658
3 mo	72.6 ± 19.6	70.5 ± 22.0	2.1 (−5.4, 9.6)	0.576
6 mo	71.9 ± 19.9	70.3 ± 23.4	1.6 (−6.2, 9.4)	0.686

*The values are given as the mean and standard deviation. Patients were asked to rate their satisfaction with treatment, as compared with their preinjection condition, using a 100-mm VAS (0 = completely dissatisfied and 100 = completely satisfied). †Between-group difference determined using independent-samples 1-way ANCOVA.

TABLE VI Adverse Events

	HYA-JOINT Plus* (N = 66)	Synvisc-One* (N = 66)	P Value
Joint pain	11 (17%)	16 (24%)	0.281
Joint swelling	5 (8%)	5 (8%)	1.000
Joint stiffness	4 (6%)	1 (2%)	0.171
Joint effusion	3 (5%)	9 (13.6%)	0.069
Limb weakness	1 (2%)	1 (2%)	1.000
Injection site paresthesia	0 (0%)	1 (2%)	0.315
Infection†	1 (2%)	1 (2%)	0.315
Back pain†	0 (0%)	1 (2%)	0.315

*The values are given as the number of patients with the percentage in parentheses. Patients are counted once for each unique adverse event and may have had >1 unique adverse event. †Judged to be unrelated to the study treatment.

Discussion

This study demonstrates that a single injection of either HYA-JOINT Plus or Synvisc-One for the treatment of knee osteoarthritis is safe and effective for 6 months. The improvement in the VAS pain score following a HYA-JOINT Plus injection was significantly greater than that after treatment with Synvisc-One at each follow-up evaluation. Several secondary outcomes also showed significant improvements for 6 months in both groups.

Petrella et al. recently compared the safety and efficacy of 1-injection formulations of 2 new hyaluronan products with those of Synvisc-One and concluded that both 1-injection regimens of 6 mL of hyaluronan were well-tolerated and relieved pain associated with knee osteoarthritis over 26 weeks[20]. Khanasuk et al. conducted a randomized trial comparing single 6-mL injections of hylan G-F 20 and Hyalgan (Fidia) for knee osteoarthritis and reported that they provided similarly improved outcomes at 26 weeks, with no adverse event related to the injected volume[21]. In our study, the reduction in the mean VAS pain score between baseline and 6 months post-injection was 33.3 mm (56.2%) in the HYA-JOINT Plus group and 23.4 mm (42.0%) in the Synvisc-One group. This degree of pain reduction appears to be clinically relevant, since a reduction in chronic pain intensity of at least 30% reflected at a least moderate clinically important difference in clinical trials of chronic pain treatments[22]. A previous meta-analysis showed a 40% to 50% reduction in pain with the use of hyaluronan compared with a placebo[11]. We also demonstrated significant superiority of HYA-JOINT Plus over Synvisc-One in terms of reducing the VAS pain score over 6 months. In addition, the accepted threshold for a minimum clinically important improvement in the WOMAC pain score, compared with baseline, in patients with osteoarthritis (12% to 18%[23]) was exceeded in our study, in which the WOMAC pain score improved, between baseline and 6 months, by 42.4% in the HYA-JOINT Plus group ($p < 0.001$) and by 35.7% in the Synvisc-One group ($p < 0.001$). The findings are consistent with the recent report by Chevalier et al., which showed a 31.3% improvement in the WOMAC pain score between baseline and 26 weeks after injection of 6 mL of hylan G-F 20[13].

Lequesne defined a score improvement of 30% to 40% at the time of follow-up as the threshold defining an effective form of treatment[24]. In our study, the improvement in the mean Lequesne index score (3.8 points; 34.2%) from baseline to 6 months was within that range of treatment effectiveness in the HYA-JOINT Plus group. The Synvisc-One group demonstrated 2.8 points (26.9%) of improvement from

baseline to 6 months, which did not meet the criterion for treatment effectiveness.

One interesting finding in this study was that one hyaluronan formulation might be better than the other depending on the patient's level of physical activity. We found that patients with an initial poor performance on the TUG test (>18.8 seconds) could benefit more, with regard to their performance at 3 months post-injection, if they were treated with HYA-JOINT Plus (Fig. 2). Similarly, patients with an initial poor performance on the SLS test could benefit more, with regard to their performance at 1 and 3 months, if they were treated with HYA-JOINT Plus (Fig. 3). Although the mechanism of the superior efficacy of HYA-JOINT Plus compared with Synvisc-One in patients with poor physical function remains unknown, we think that the excessive capsular distension caused by the volume effect of Synvisc-One might affect patients' physical activity. Additional studies are needed to identify the characteristics of patients most likely to benefit from hyaluronan, and more predictors of a good response have yet to be defined.

In our study, most adverse events were mild and self-limiting, suggesting a favorable safety profile of both products. Previously reported adverse reactions to hyaluronan include pain and swelling at the injection site in up to 20% of patients[25,26]. Acute pseudoseptic reactions have been reported in about 2% to 8% of patients injected with Synvisc[26-28]. Yan et al. reported mild and self-limiting adverse events in 16.4% of Chinese patients who had undergone injection of 6 mL of hylan G-F 20[29]. In comparison, a trial of Hyalgan demonstrated a rate of injection-site pain of 23%[30]. SUPARTZ (Seikagaku) was reported to be associated with an arthralgia rate of 17.8%[31]. Whether the adverse events were caused by the injected hyaluronan itself or the injection technique, a contaminant of the purification process, or a component of the hyaluronan carrier substance is unknown. Additional studies are needed to differentiate the source of the adverse events. The optimal composition of hyaluronan has yet to be defined.

Our study had several limitations. First, it was performed at a single center, and only patients with Kellgren-Lawrence grade-2 or 3 tibiofemoral osteoarthritis were recruited. The results cannot be generalized to all osteoarthritis populations with different degrees of radiographically evident severity. Second, because of differences in viscosity, volume, and marketed packaging between the 2 hyaluronan products, the physician who performed the injections could not be blinded. However, that physician was not involved in the outcome assessments. Third, we did not have a placebo group. Since joint injections have a strong placebo effect, which may reduce pain by nearly 30% during the first few weeks[32], we may have overestimated the real effects of both products. However, because the placebo effect would have been the same for both groups and mostly seen in the early periods, the findings of this study at 3 and 6 months may reflect reliable results for both hyaluronan injections. Fourth, differences in the dosage and volume of intra-articular hyaluronan formulations could affect outcomes. The possibility of a dose-dependent response that could increase efficacy should be studied in the future. Finally, we did not use imaging to document that the injections were truly intra-articular.

In conclusion, this trial shows that a single injection of either HYA-JOINT Plus or Synvisc-One is effective and safe for the treatment of knee osteoarthritis over 6 months. HYA-JOINT Plus is superior to Synvisc-One in terms of reduction of VAS pain and WOMAC stiffness scores at 6 months. Additional studies to elucidate the mechanism of this possible superiority are warranted. The cost-effectiveness of single-injection regimens of hyaluronan should be explored.

Appendix

eA A description of the HYA-JOINT Plus and Synvisc-One cross-linking and of the secondary outcome measures is available with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/A148). ■

Shu-Fen Sun, MD[1,2]
Chien-Wei Hsu, MD[1,2,3]
Huey-Shyan Lin, PhD[3]
I-Hsiu Liou, MD[1]
Yin-Han Chen, MD[1]
Chia-Ling Hung, MD[1]

[1]Department of Physical Medicine and Rehabilitation (S.-F.S., I-H.L., Y.-H.C., and C.-L.H.) and Department of Internal Medicine (C.-W.H.), Kaohsiung Veterans General Hospital, Kaohsiung City, Taiwan

[2]National Yang-Ming University School of Medicine, Taipei City, Taiwan

[3]School of Nursing, Fooyin University, Kaohsiung City, Taiwan

E-mail address for S. Sun: sfsun.tw@yahoo.com.tw

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