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ORIGINAL RESEARCH

Effects of Intra-articular Coinjections of Hyaluronic Acid and Hypertonic Dextrose on Knee Osteoarthritis: A Prospective, Randomized, Double-Blind Trial

Ru-Lan Hsieh, MD,[a,b] Wen-Chung Lee, MD, PhD[c]

From the [a]Department of Physical Medicine and Rehabilitation, Shin Kong Wu Ho-Su Memorial Hospital, Taipei; [b]Department of Physical Medicine and Rehabilitation, School of Medicine, College of Medicine, Taipei Medical University, Taipei; and [c]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan.

Abstract

Objective: To determine whether intra-articular coinjection with hypertonic dextrose improves the outcome of hyaluronic acid (HA) prolotherapy for knee osteoarthritis (OA).

Design: Prospective, randomized, double-blind trial.

Setting: Medical center in Taiwan.

Participants: In total, 104 participants who fulfilled the American College of Rheumatology clinical and radiographic criteria for knee OA with a Kellgren-Lawrence score of 2 or 3 were recruited (N=104).

Interventions: The participants were blocked randomized to the treatment (HA and hypertonic dextrose) or control (HA and normal saline) group. Ultrasound-guided knee intra-articular injections were administered once a week for 3 weeks.

Main Outcome Measures: The primary outcomes were performance-based physical function measures (regular and fastest walking speed, stair climbing time, and chair rising time), and the secondary outcomes were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee Injury and Osteoarthritis Outcome Score (KOOS). The outcome measures were assessed before the injections and at 1 week and 1, 3, and 6 months after the injections. The data were analyzed through repeated-measures analysis of covariance.

Results: Significant intergroup difference-in-differences favoring the treatment group were observed for improvements in stair climbing time (−1.6; 95% confidence interval, −8.56 to 4.16; *P*=.38) and WOMAC physical function (−21.2; 95% confidence interval, −126.05 to 103.83; *P* = .045) at 6 months. The group×time interaction effects favored the treatment group for regular (*P*=.001) and fastest walking speed (*P*=.001) and chair rising time (*P*=.038); WOMAC stiffness (*P* < .001) and physical function (*P* = .003); and KOOS for pain (*P* = .035), other symptoms (*P*=.022), and quality of life (*P*=.012).

Conclusions: Compared with HA plus normal saline coinjections, HA plus dextrose coinjections resulted in more significant improvements in stair climbing time and physical function at 6 months, effectively decreased pain, and improved physical function and physical functional performance from 1 week to 6 months. HA plus dextrose coinjections could be a suitable adjuvant therapy for patients with knee OA.

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Osteoarthritis (OA) is the leading cause of disability among older adults.[1] The estimated worldwide prevalence of radiographically confirmed symptomatic knee OA is 3.8% (>10% in adults 60 years),[2] and the adverse effects of OA on patients' physical functions, quality of life (QOL), and finances are increasing.[3]

Opioid and anti-inflammatory medications can cause adverse effects in patients with knee OA. Therefore, nonsurgical

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treatments using injectable agents (eg, corticosteroids, hyaluronic acid [HA], prolotherapy agents) are widely administered for knee OA because they have fewer adverse effects, are less invasive, and are less expensive than total knee arthroplasty.[3] Possible mechanisms underlying the effectiveness of HA in the treatment of knee OA include (1) a mechanical effect produced by lubrication and shock absorption; (2) endogenous HA production; (3) proteoglycan and glycosaminoglycan synthesis; (4) chondroprotection owing to CD44 binding to inhibit interleukin (IL)-1β and matrix metalloproteinase production; (5) an analgesic effect produced by the interaction of free nerve endings and HA receptors within the joint; and (6) an anti-inflammatory effect achieved by suppressing IL-1β, IL-6, IL-8, prostaglandin E2, and tumor necrosis factor.[4-6] The possible mechanisms underlying the effectiveness of prolotherapy in the treatment of knee OA include (1) the opening of potassium channels to reduce nociceptive fiber pain transmission and pain perception[1,7,8]; (2) the stimulation of joint tissue healing through the induction of an inflammatory response recruiting growth factors, cytokines, and other chemical mediators[3,7,8-14]; (3) the blocking of Na^+ and Ca^+ influx to reduce nociception and substance P release and minimize edema and neuropathic pain[15]; and (4) the expansion of local tissues and needle trauma, which induce tissue-level effects.[16,17]

Pain in knee OA has a multifactorial etiology.[16] Despite the use of many pain management methods, some patients may continue to experience pain.[1] Thus, more effective therapies with a lower risk of harm, such as a combination of injectable agents, should be developed as alternatives.[1] However, to our knowledge, the combined therapeutic effects of HA and prolotherapy (such as that with dextrose) on knee OA have not been investigated. Therefore, we investigated whether coinjection of dextrose and HA offers additional benefits because of their different mechanisms. We hypothesized that patients with knee OA receiving HA and dextrose coinjections would exhibit more significant improvements in knee-related pain scores, physical function, and physical functional performance than those receiving HA and normal saline coinjections because of the additional regenerative effects of the prolotherapy agent.

Methods

Study design

This study employed a prospective, randomized, double-blind design that followed the Consolidated Standards of Reporting Trials guideline and was approved by the Institutional Review Board for the Protection of Human Subjects of Shin Kong Wu Ho-Su Memorial Hospital in Taipei, Taiwan. Written consent was obtained from each participant after the study protocol had been explained in detail. This study was conducted from August 2017 to July 2019, and the participants were followed up for 6 months. The study was registered at ClinicalTrials.gov (NCT03238183).

List of abbreviations:

HA	**hyaluronic acid**
IL	**interleukin**
KOOS	**Knee Injury and Osteoarthritis Outcome Score**
MCID	**minimal clinically important difference**
OA	**osteoarthritis**
QOL	**quality of life**
WOMAC	**Western Ontario and McMaster Universities Osteoarthritis Index**

Participants

Participants were recruited from the Department of Physical Medicine and Rehabilitation clinic of Shin Kong Wu Ho-Su Memorial Hospital. The inclusion criteria were as follows: age of 40-85 years, knee OA diagnosis satisfying the American College of Rheumatology clinical and radiographic criteria, Kellgren-Lawrence scores of 2 or 3 determined by radiographs (standing anteroposterior views of both knees), the ability to undergo 3 weeks of treatment and 6 months of follow-up, and agreement to avoid nonsteroidal anti-inflammatory drugs during the research (acetaminophen was prescribed for intractable pain). The exclusion criteria were as follows: a self-reported history of knee surgery, fracture, or infection; pregnancy or plans for pregnancy; malignant neoplasms; neurologic deficits, including a history of vertigo or stroke; autoimmune disease; a history of intra-articular knee injections of HA or prolotherapy within 6 months; or other therapies for knee OA.

Baseline clinical assessment

Basic information, including age, sex, educational level, marital status, occupational status, smoking and drinking habits, and comorbidities, was collected, and body mass index was calculated.

Primary outcome

Physical functional performance was assessed using the 10-m walk (regular and fastest pace), stair climbing, and chair rising tests. The 10-m walk test measures the regular and fastest speed at which an individual can walk 10 m across a flat surface. The stair climbing test measures the minimal time required to climb and descend a flight of stairs (14 steps with 18-cm heights). The chair rising test measures the minimal time needed to rise 5 times from a standard chair to a standing position without support. A longer time to complete these tests reflects the more significant limitation of physical functional performance. The minimal clinically important difference (MCID) is 0.1-0.2 m/s for the 10-m walk test,[18,19] 1 second for the stair climbing test,[20] and 2.5 seconds for the chair rising test.[21]

Secondary outcomes

The Chinese version of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC)[22] visual analog scale was used to assess pain, stiffness, and physical function, whose possible scores range from 0 to 500, 200, and 700, respectively. Higher scores represent more severe symptoms and functional limitations. The reliability and validity of the index are excellent.[23] The MCIDs are 8.74, 20.24, and 14.48 for the pain, stiffness, and physical function subscales, respectively.[24] The Chinese version of the Knee Injury and Osteoarthritis Outcome Score (KOOS) instrument measured knee OA-related pain, function, disability, and QOL; the instrument has acceptable reliability and validity.[25,26] Five subscales, namely, pain, other symptoms, functions in daily life, sports and recreation, and knee-related QOL, were obtained. The possible scores range from 0-100, with higher scores

representing fewer symptoms and greater function. The MCID for knee OA in KOOS remains unreported.[27]

Randomization

After completing the primary data collection and assessments above, the patients were randomly allocated to the treatment (HA plus hypertonic dextrose coinjections) or the control group (HA plus normal saline coinjections). Block randomization (with a block size of 4) was applied using a computer-generated random number table. The participants were allocated to their groups with sealed opaque envelopes containing the group assignment, and these were opened in the same order to avoid selection bias.

Interventions

The participants were placed in the supine position and had their skin carefully sterilized. After the aseptic preparation, an ultrasound-guided injection was administered with a 21-gauge needle to the lateral suprapatellar pouch through the in-plane approach (Philips Ultrasound System[a]). The treatment group received a 7-mL 25% dextrose injection (3.5mL of 50% dextrose mixed with 3.5mL of 2% lidocaine) followed by a 2-mL 10 mg/dL HA injection (Hyruan Plus,[b] molecular weight: 3000kDa) with the same needle. The control group received a 7-mL injection of 3.5 mL of normal saline with 3.5 mL of 2 %lidocaine followed by a 2-mL 10 mg/dL HA injection using the same needle. The research assistant prepared all the solutions and wrapped the syringes in silver-colored paper. All of the injection procedures were performed by the same senior physiatrist in a blinded manner, who had more than 10 years of experience in administering ultrasound-guided injections. The participants were unaware of their assigned group and blinded to the injectate. Each participant received 3 coinjections at weeks 1, 2, and 3.

Follow-up assessment

An investigator blinded to the group allocation evaluated physical functional performance, scores of WOMAC and KOOS at 5 time points: before treatment; 1 week after treatment termination (ie, 1 week after the last injection); and 1, 3, and 6 months after treatment termination. The primary outcome time point was 6 months after treatment.

Sample size

Sample size calculation was based on a randomized controlled trial that evaluated the repeated intra-articular coinjections of hyaluronic acid (HA) plus corticosteroids and HA alone for knee OA.[28] The mean ± SD difference of fastest walking time for 10 m at 1 month compared with baseline was 3±1.78 seconds for the coinjections group and 2±1.8 seconds for the HA group, respectively. [28] Assuming a pooled SD of 1.8, a total of 52 participants in each group had 80% power to detect a significant effect size of 0.56 in a 2-sample t test with an α set at 0.05.

Statistical methods

The results are expressed as means ± SDs. The demographic data and baseline scores of the groups were analyzed using t or chi-square tests. Paired and 2-sample t tests were used to compare the improvement of scores at each follow-up with the baseline scores and those of the other group. Repeated-measures analysis of covariance was used to test the group×time interaction effects at the 4 follow-up assessments, with the baseline data serving as the covariates. The independent variable was the treatment administered (HA plus dextrose or HA plus normal saline). The dependent variables were the improvements in physical functional performance and scores of WOMAC and KOOS at the 5 measurement times (baseline, 1 week, and 1, 3, and 6 months). Intention-to-treat analysis (last observation carried forward) was performed to estimate missing data. We used SAS v9.4,[c] and $P<.05$ indicated statistical significance.

Table 1 Demographic data and baseline scores of study participants

Variable/Group	Treatment (n=52)	Control (n=52)	*P* Value
Sex, n (%)			.982
Male	11 (21)	12 (23)	
Female	41 (79)	40 (77)	
Age (y), mean ± SD	62.4±10.4	62.8±9.7	.981
Height (cm), mean ± SD	156.7±8.5	157.0±9.4	.763
Weight (kg), mean ± SD	65.9±11.6	64.5±15.5	.855
BMI, mean ± SD	27.2±5.4	26.1±4.5	.925
Marital status (n)			.787
Single	2	5	
Married	50	44	
Divorced	0	3	
Education (n)			.720
Below 12th grade	34	38	
Above 12th grade	18	14	
Comorbidity, n (%)			.850
Yes	24 (46)	26 (50)	
No	28 (54)	26 (50)	
Smoking (n)			.972
Never	49	48	
Ever	2	2	
Current	1	2	
Alcohol consumption (n)			.824
Never	49	52	
Current	3	0	
Kellgren-Lawrence grade (n)			.690
II	15	18	
III	37	34	
Physical functional performance			
Regular walking speed (m/s)	0.8929	0.9174	.328
Fastest walking speed (m/s)	1.1236	1.0526	.507
Stair ascent time (s)	21.5	22.1	.182
Stair descent time (s)	24.3	25.5	.051
Chair rising time (s)	20.5	21.4	.062
WOMAC			
Pain	230.8	216.9	.138
Stiffness	100.4	105.2	.581
Physical function	523.5	513.5	.377
KOOS			
Pain	40.9	42.5	.410
Other symptoms	38.5	37.5	.655
Activities of daily living	45.5	39.2	.104
Sports & recreation	19.5	18.8	.895
Quality of life	20.7	19.0	.389

NOTE. Treatment group, hyaluronic acid plus dextrose; Control group, hyaluronic acid plus normal saline.
Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

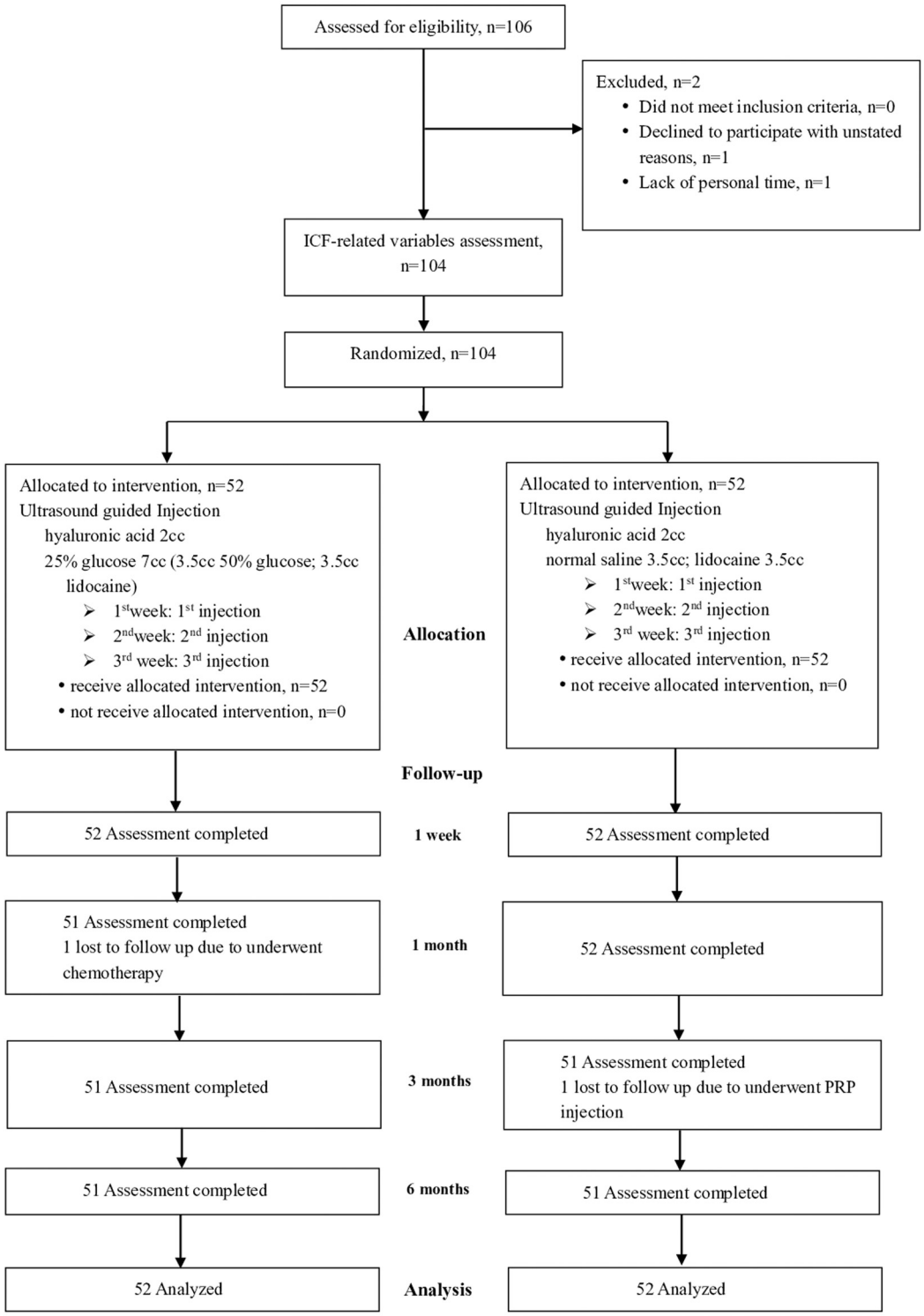

Fig 1 Flowchart. Abbreviations: ICF, International Classification of Functioning, Disability and Health.

Results

A total of 106 participants were included; 1 potential participant declined to participate for personal reasons, another was excluded for unstated reasons, and 104 participants completed the initial assessment. Ultimately, each group comprised 52 participants. No significant differences were observed between the 2 groups in age, sex, marital status, educational level, comorbidities, smoking or drinking habits, body mass index, or Kellgren-Lawrence score (table 1). The pretreatment physical functional performance and scores of WOMAC and KOOS did not differ significantly between the groups (table 1). One participant in the treatment group dropped out of the study 1 month after receiving the third injection because of cancer and chemotherapy. One participant in the

Table 2 Comparison of changes of improvement in primary outcome

Variable/Group	Treatment (n=52)		Control (n=52)		Between-Group Difference			Group × Time
	Mean ± SD	MD	Mean ± SD	MD	MD	95% CI	*P* Value	*P* Value
Physical functional activity								
Regular walking speed (m/s)								.001*
T0	0.8929±0.3215		0.9174±0.3670					
T1	0.9434±0.2659	0.050	0.9524±0.3810	0.035	0.016	−0.14 to 0.12	.005	
T2	0.9804±0.3650	0.088	1.0000±0.4000	0.083	0.005	−0.17 to 0.13	.340	
T3	0.9901±0.4595	0.097†	0.9804±0.3922	0.063	0.034	−0.16 to 0.18	.001‡	
T4	0.9524±0.4211	0.059†	0.9434±0.3774	0.026	0.033	−0.15 to 0.16	<.001‡	
Fastest walking speed (m/s)								.011*
T0	1.1236±0.5618		1.0526±0.5263					
T1	1.1628±0.5814	0.039	1.0870±0.5435	0.034	0.005	−0.14 to 0.29	.175	
T2	1.1905±0.5952	0.067	1.1111±0.5556	0.059	0.008	−0.14 to 0.30	.171	
T3	1.2658±0.6329	0.142	1.1236±0.5618	0.071	0.071	−0.09 to 0.38	<.001‡	
T4	1.1765±0.5882	0.053	1.0638±0.5319	0.011	0.042	−0.11 to 0.33	<.001‡	
Stair ascent time (s)								.051
T0	21.5±14.5		22.1±15.9					
T1	20.9±16.1	−0.6	21.9±16.2	−0.2	−0.4	−7.28 to 5.28	.482	
T2	20.0±15.4	−1.5	20.5±14.8	−1.6	0.1	−6.37 to 5.37	.889	
T3	19.5±14.9	−2.0	19.9±15.4	−2.2	0.2	−6.29 to 5.49	.807	
T4	19.6±16.0	−1.9	21.8±16.7	−0.3	−1.6	−8.56 to 4.16	.038‡	
Stair descent time (s)								.053
T0	24.3±19.6		25.5±19.2					
T1	22.5±18.4	−1.8	24.7±19.1	−0.8	−1.0	−9.49 to 5.09	.395	
T2	22.1±18.6	−2.2	23.2±18.4	−2.3	0.1	−8.27 to 6.13	.469	
T3	21.8±17.5	−2.5	22.5±17.5	−3.0	0.5	−7.53 to 6.08	.500	
T4	24.0±18.1	−0.3	24.0±17.8	−1.5	1.2	−6.93 to 7.03	.453	
Chair rising time (s)								.038*
T0	20.5±12.6		21.4±12.4					
T1	19.0±10.5	−1.5	21.0±11.5	−0.4	−1.1	−6.28 to 2.28	<.001‡	
T2	18.0±11.1	−2.5	19.4±10.3	−2.0	−0.5	−5.57 to 2.77	.060	
T3	18.1±10.6	−2.4	18.7±11.3	−2.7	0.3	−4.86 to 3.66	.095	
T4	19.2±12.5	−1.3	19.5±11.0	−1.9	0.6	−4.88 to 4.28	.023‡	

NOTE. Treatment group, hyaluronic acid plus dextrose; Control group, hyaluronic acid plus normal saline.
Abbreviations: CI, confidence interval; MD, mean difference; T0, time point before treatment; T1, time point after 1 wk of treatment; T2, time point after 1 mo of treatment; T3, time point after 3 mo of treatment; T4, time point after 6 mo of treatment.
* *P*<.05, repeated-measures analysis of covariate, group×time interaction.
† *P*<.05, comparison of improvement with baseline, intragroup.
‡ *P*<.05, comparison of mean difference (95% CI) of improvement with baseline, intergroup.

control group had local swelling after the third injection, which improved after 3 days of ice pack application. Three months after the injections, the patient underwent platelet-rich plasma injection at another hospital. The dropout rate was thus 1.9%. The 2 participants who dropped out were counted in the trial reporting and included in the outcome assessment through the intention-to-treat method (fig 1). One patient in each group had effusion and thus received puncture aspiration before the injections. Except for the patient with local swelling, no local or systemic adverse effects were observed during or after the treatment.

For the primary outcomes, we found significant intergroup difference-in-difference at 6 months in regular walking speed (*P*<.001), fastest waking speed (*P*<.001), stair ascent time (*P*=.038), and chair rising time (*P*=.023). Among them, stair ascent time (−1.6; 95% confidence interval, −8.56 to 4.16; *P*=.38) was the only significant intergroup difference-in-difference favoring the treatment group at 6 months; it exhibited improvement greater than those of the control group that exceeded the MCID of 1 second (table 2). Group×time interaction effects favoring the treatment group in regular walking speed (*P*=.001), fastest walking speed (*P*=.011), and chair rising time (*P*=.038) were observed (see table 2, fig 2A). For the secondary outcomes, we found significant intergroup difference-in-difference at 6 months in WOMAC stiffness (*P*=.044) and physical function (*P*=.045) and KOOS pain (*P*=.001). Among them, the only significant intergroup difference-in-difference favoring the treatment group at 6 months was WOMAC physical function (−21.2; 95% confidence interval; −126.05 to 103.83; *P*=.045), with the difference exceeding the MCID (14.48) (table 3). The group×time interaction effects favored the treatment group in WOMAC stiffness (*P*<.001) and physical function (*P*=.003) and KOOS for pain (*P*=.035), other symptoms (*P*=.022), and QOL (*P*=.012) (see table 3, figs 2B, C).

Discussion

We compared the effects of intra-articular coinjection of HA with either hypertonic dextrose or normal saline on knee OA. We found significantly more improvements in the HA plus dextrose group than in the HA plus normal saline group in stair climbing time and physical function at 6 months, and these differences were

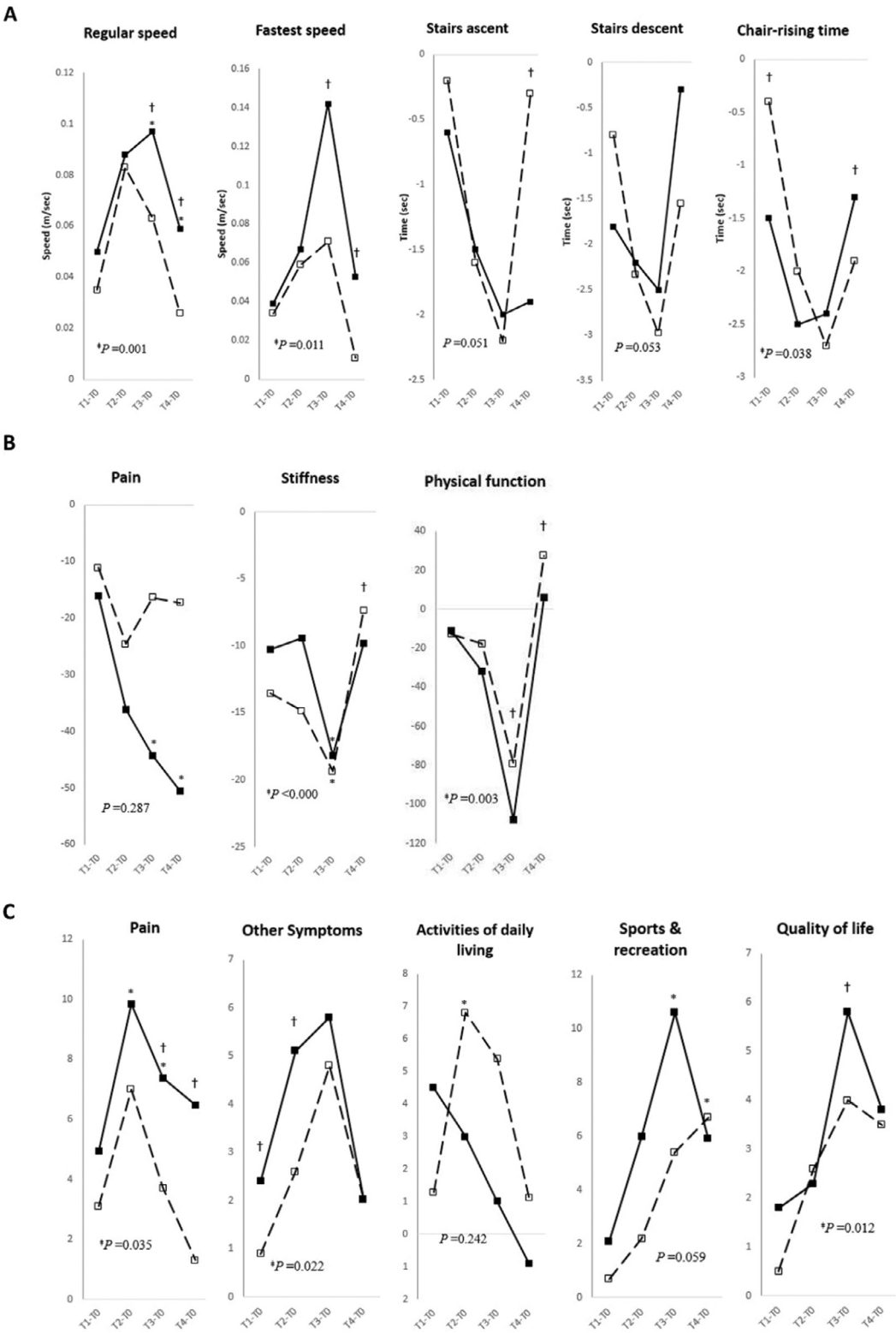

Fig 2 Improvement of physical functional performance, WOMAC, and KOOS. (A) Physical functional performance, (B) WOMAC, (C) KOOS. Solid square, treatment group; hallow square, control group. *P<.05, comparison of improvement with baseline, intragroup. †P<.05, comparison of mean difference (95 % confidence interval) of improvement with baseline, intergroup. ‡P<.05, repeated-measures analysis of covariate, group-×time interaction. Abbreviations: T_0, time point before treatment; T_1, time point after 1wk of treatment; T_2, time point after 1 mo of treatment; T_3, time point after 3 mo of treatment; T_4, time point after 6 mo of treatment.

Table 3 Comparison of changes of improvement in secondary outcomes.

	Treatment (n=52)		Control (n=52)		Between-Group difference			Group×Time
Variable/ Group	Mean ± SD	MD	Mean ± SD	MD	MD	95% CI	*P* Value	*P* Value
WOMAC								
Pain								.287
T0	230.8±97.9		216.9±89.4					
T1	214.7±85.1	−16.1	205.8±95.9	−11.1	−5.0	−26.38 to 44.18	.460	
T2	194.7±94.4	−36.1	192.4±76.9	−24.6	−11.5	−31.14 to 35.84	.198	
T3	186.6±92.1	−44.2*	200.6±93.4	−16.4	−27.9	−50.07 to 22.09	.121	
T4	180.3±77.9	−50.5*	199.6±91.9	−17.3	−33.2	−52.46 to 13.81	.073	
Stiffness								<.001†
T0	100.4±40.6		105.2±39.6					
T1	90.1±44.6	−10.3	91.6±40.6	−13.6	3.3	−18.12 to 15.08	.252	
T2	91.0±45.3	−9.4	90.3±40.8	−14.9	5.5	−16.09 to 17.43	.229	
T3	82.2±41.5	−18.2*	85.8±39.8	−19.4*	1.2	−19.46 to 12.19	.383	
T4	90.6±40.6	−9.8	97.8±42.8	−7.4	−2.4	−23.45 to 8.99	.044‡	
Physical function								.003†
T0	523.5±318.1		513.5±326.8					
T1	512.8±303.9	−10.7	500.8±330.0	−12.7	2.0	−111.39 to 135.39	.779	
T2	491.9±287.2	−31.6	495.8±295.5	−17.7	−13.9	−117.21 to 109.47	.220	
T3	415.6±299.6	−107.9	434.3±301.2	−79.1	−28.8	−135.59 to 98.12	.038‡	
T4	529.8±292.7	6.3	540.9±298.2	27.4	−21.2	−126.05 to 103.83	.045‡	
KOOS								
Pain								.035†
T0	40.9±16.5		42.5±19.5					
T1	45.9±17.4	5.0	45.6±19.0	3.1	1.9	−6.83 to 7.34	.165	
T2	50.8±18.2	9.9*	49.5±17.4	7.0	2.9	−5.67 to 8.18	.068	
T3	48.3±17.5	7.4*	46.2±18.5	3.7	3.7	−4.92 to 9.09	.013‡	
T4	47.4±19.5	6.5	43.8±20.5	1.3	5.2	−4.20 to 11.37	.001‡	
Other symptoms								.022†
T0	38.5±16.2		37.5±20.0					
T1	40.9±17.5	2.4	38.4±19.5	0.9	1.5	−4.71 to 9.71	.040‡	
T2	43.6±17.0	5.1	40.1±18.6	2.6	2.5	−3.43 to 10.43	.027‡	
T3	44.3±18.5	5.8	42.3±18.5	4.8	1.0	−5.20 to 9.20	.323	
T4	40.5±18.0	2.0	39.5±19.5	2.0	0.0	−6.30 to 8.30	.998	
Activities of daily living								.242
T0	45.5±19.2		39.2±18.4					
T1	50.0±15.8	4.5	40.5±15.5	1.3	3.2	3.42 to 15.61	.109	
T2	48.5±18.6	3.0	46.0±15.4	6.8*	−3.8	−4.15 to 9.14	.096	
T3	46.5±18.0	1.0	44.6±19.5	5.4	−4.4	−5.38 to 9.21	.085	
T4	44.6±19.7	−0.9	40.3±15.1	1.1	−2.0	−2.55 to 11.08	.222	
Sports & recreation								.059
T0	19.5±15.5		18.8±13.9					
T1	21.6±14.0	2.1	19.5±15.1	0.7	1.4	−3.56 to 7.76	.296	
T2	25.5±15.4	6.0	21.0±14.2	2.2	3.8	−1.26 to 10.26	.282	
T3	30.1±13.5	10.6*	24.2±15.6	5.4	5.2	0.23 to 11.57	.153	
T4	25.4±15.0	5.9	25.5±13.4	6.7*	−0.8	−5.63 to 5.43	.212	
Quality of life								.012†
T0	20.7±17.2		19.0±18.2					
T1	22.5±17.5	1.8	19.5±17.9	0.5	1.3	−3.89 to 9.89	.064	
T2	23.0±16.9	2.3	21.6±16.8	2.6	−0.3	−5.15 to 7.95	.609	
T3	26.5±15.4	5.8	23.0±15.9	4.0	1.8	−2.59 to 9.59	.027‡	
T4	24.5±16.0	3.8	22.5±19.1	3.5	0.3	−4.85 to 8.85	.665	

NOTE. Treatment group, hyaluronic acid plus dextrose; Control group, hyaluronic acid plus normal saline.

Abbreviations: CI, confidence interval; MD, mean difference; T0, time point before treatment; T1, time point after 1 wk of treatment; T2, time point after 1 mo of treatment; T3, time point after 3 mo of treatment; T4, time point after 6 mo of treatment.

* *P*<.05, comparison of improvement with baseline, intragroup.

† *P*<.05, repeated-measures analysis of covariate, group×time interaction.

‡ *P*<.05, comparison of mean difference (95% CI) of improvement with baseline, intergroup.

clinically meaningful. Furthermore, the HA plus dextrose coinjections exerted more excellent group×time interaction effects on pain, stiffness, other symptoms, physical function, regular and fastest walking speed, chair rising time, and QOL than HA plus normal saline coinjections. No severe adverse effects occurred for both treatments, and high adherence was observed.

Patient-reported outcome measures are recommended for pain, physical function, and global assessment in knee OA.[29] Knee OA is accompanied by limitations in the performance of daily activities, such as walking on level ground, rising from a chair, and climbing stairs.[30,31] Patient-reported and performance-based measures capture different aspects of physical function.[32] Patient-reported measures fail to accurately capture changes in functional status because they are more likely to represent the patients' experience in performing rather than their ability to perform relevant activities.[20] Pain and physical function are different concepts, and the interventions that address these issues differ.[20,32] Standard performance-based tests of physical function for knee OA include the chair rising, fast 10-m walk, stair climbing, timed Up and Go, and 6-minute walk tests; the first 3 tests are the minimum core set for performance-based physical function evaluation in OA.[32] Therefore, we used these core tests as our primary outcomes.

A single HA injection (such as Hylan G-F 20) is effective and safe for relieving pain.[33] However, such treatment remains unavailable in Taiwan. A course of repeated intra-articular HA injections reduces pain through anti-inflammatory, lubricative, and chondroprotective effects.[34,35] It is a safe therapeutic option for knee OA.[35] HA of different molecular weights may have different efficacies.[36] Compared with low-molecular-weight HA, high-molecular-weight HA (≥3000 kDa)[33] has greater proteoglycan synthesis capacity, anti-inflammatory effects, and joint lubrication effects and achieves more significant maintenance of viscoelasticity.[4,5,36,37] Furthermore, traditional avian-derived HA products may cause local adverse reactions.[38-40] Therefore, we used a high-molecular-weight HA product produced derived from bacteria (Hyruan Plus: 3000 kDa) in this study; this product should be administered as 3 consecutive weekly intra-articular injections.

One to 4 hypertonic dextrose injections can be administered weekly or up to 4 weeks apart, with doses of 1-8 mL at concentrations of 10%-30%.[41-43] Although monthly dextrose injections are the most common,[16] Hyruan Plus should be administered once a week for 3 consecutive weeks. Therefore, we also administered all 3 dextrose injections at 1-week intervals. The standard dextrose prolotherapy for knee OA involves intra-articular injection and multiple periarticular injections into soft tissue bony attachments.[15] The numerous injections and occasional postinjection soreness of these periarticular injections are clinical problems because they may reduce patient compliance.[44,45] Intra-articular dextrose injection reduces pain and improves function in knee OA,[15] exhibiting effects comparable with those of periarticular injections.[46] Therefore, we administered intra-articular dextrose injections in the present study. Only 1 of our participants developed local swelling after the injections, and that patient experienced no severe adverse events. Our dropout rate was 1.9%. Similar to those of previous studies, our results indicate that intra-articular injection is rapid, straightforward, and safe and results in high patient adherence.[15,47,48]

Although standard protocols do not call for the local anesthetic to be added to HA or dextrose injections, some studies have added lidocaine.[7,49,50] Because of the possibility that both injections together would be intolerable, we added lidocaine as a local anesthetic to our coinjections. The time to onset of action of 2% lidocaine is 1-2 minutes, and its effects persist for 1 hour even at the maximal recommended volume of 10 mL.[51] Therefore, some short-term outcomes (1 week and 1 month after injections) were unlikely because of a local anesthetic effect. In vitro experimental and in vivo animal studies have demonstrated dose-dependent and time-dependent chondrotoxic effects of local anesthetics such as lidocaine.[52,53] However, results obtained for chondrocyte cultures or animal models might not be transferrable to human tissues.[52] A recent in vivo study demonstrated that a single intra-articular injection of 10 mL of 2% lidocaine did not affect chondrocyte viability in osteoarthritic or healthy knee cartilage.[54] Therefore, the intra-articular chondrotoxicity of 3.5 mL of 2% lidocaine observed in the present study might be negligible.

Study strengths and limitations

The strength of the present study is the administration of intra-articular injections under ultrasound guidance, which ensured accurate intra-articular needle placement[55]; the knee intra-articular injection protocol is easy to learn and requires <10 minutes under ultrasonic guidance.[43] Hypertonic dextrose prolotherapy can be performed in an outpatient setting because of its simple procedure that does not require the use of expensive solutions.[43] Finally, the subjective patient-reported and objective performance-based measures we used to assess knee OA-related pain, physical function, and physical functional performance are valid and reliable.

Several study limitations must be noted. First, our sample size was relatively small. Second, the follow-up duration was short. Therefore, the long-term (≥1 year) therapeutic and adverse effects could not be assessed. However, the effects of HA persist for 6 months; therefore, we used a 6-month follow-up period. Third, we recruited our participants from only a single medical center. Therefore, further studies using a community-based cohort should be conducted to test the generalizability of our results. Fourth, the optimal volume, concentration, interval, number, and site (intra-articular vs periarticular) for hypertonic dextrose injections warrant further study.[16] Fifth, because quantitative evidence has indicated the effectiveness of dextrose prolotherapy,[16,47] we did not include a dextrose-only group. Including such a group in future study designs may provide insightful results. Sixth, we did not evaluate the effects of changes in joint cartilage. Therefore, further studies using radiographic, ultrasonic, or magnetic resonance imaging should be conducted. Seventh, normal saline, rather than a placebo, has been used as an active control in knee OA injection trials[47,56] because it achieves a clinically meaningful therapeutic response.[56] Therefore, we did not include a control group receiving only HA. Finally, we did not assess the effects on inflammatory biomarkers.

Conclusions

Intra-articular coinjections of HA and hypertonic dextrose improved stair climbing time and physical function after 6 months more than HA and normal saline did. The group×time interaction effects favoring the HA and hypertonic dextrose coinjections were observed on regular and fastest walking speed, chair rising time, pain, stiffness, other symptoms, physical function, and QOL. The effects persisted for 6 months after the final injection. Prolotherapy is a simple, safe, and inexpensive treatment modality and can easily be administered in clinical settings. Therefore, HA and dextrose coinjections can improve standard care and provide adjuvant therapy for patients with knee OA.

Suppliers

a. Philips Ultrasound System; EPIQ 5.
b. Hyruan Plus; LG Life Sciences.
c. SAS v9.4; SAS Institute.

Keywords

Glucose; Hyaluronic acid; Osteoarthritis, knee; Prolotherapy; Rehabilitation

Corresponding author

Ru-Lan Hsieh, MD, Department of Physical Therapy and Rehabilitation, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, No. 95, Wenchang Rd, Shi-Lin Dist, Taipei City 11101, Taiwan.
E-mail address: M001052@ms.skh.org.tw.

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