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# Origin and Efficacy of Hyaluronan Injections in Knee Osteoarthritis: Randomized, Double-Blind Trial

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

AB **Yuanli Guo**  
CDG **Peiyan Yang**  
EF **Liu Liu**

Department of Orthopedics, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, P.R. China

**Corresponding Author:** Liu Liu, e-mail: LauermanRalip@yahoo.com  
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**Background:** Several hyaluronan preparations are available that have different dosage forms, origins, and concentrations. The objective of the study was to compare the efficacy of intra-articular chemically cross-linked hyaluronan (CCH) and avian-derived hyaluronan (ADH) injections in knee osteoarthritis (KOA) patients.





**Material/Methods:** In total, 258 patients were randomized into 2 groups of 129 each: patients who received CCH injection (CCH group) and patients who received ADH injection (ADH group). Radiographic Kellgren-Lawrence score, visual analog scale (VAS) pain score, Lequesne index score, the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index, single-limb stance (SLS) test, and timed "Up-and-Go" (TUG) test were performed. The Mann-Whitney U test or independent *t*-test following Bonferroni adjustment was performed for statistical analysis at 95% of confidence level.

**Results:** The CCH group had improved VAS pain score ( $P<0.0001$ ,  $q=54.803$ ), total WOMAC score ( $P<0.0001$ ,  $q=4.753$ ), Lequesne index score ( $P<0.0001$ ,  $q=3.208$ ), and SLS time ( $P<0.0001$ ,  $q=8.76$ ) at the end of 6 months as compared to those in the ADH group. After 6 months of follow-up, the ADH group had improved TUG time ( $P=0.0148$ ,  $q=3.385$ ) as compared to baseline. Both groups of patients had the similar improvement in Kellgren-Lawrence score and mild to moderate adverse effects after 6 months.

**Conclusions:** CCH injection was superior to ADH injection.

**MeSH Keywords:** **Hyaluronic Acid • Knee Joint • Osteoarthritis • Osteoarthritis, Knee • Viscosupplementation • Visual Analog Scale**

**Full-text PDF:** <https://www.medscimonit.com/abstract/index/idArt/908797>

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## Background

Osteoarthritis (OA) can cause disability, pain, and restriction of mobility [1]. Cartilage attrition, subchondral bone remodeling, osteophyte formation, and synovial inflammation are common characteristics of OA [2]. Chondrosenescence is associated with inflammation, disturbed interplay between autophagy and inflammasomes, a decrease in the efficacy of articular cartilage repair, and the prevalence of osteoarthritis [3]. Recombinant lubricin treatment protects articular cartilage and prevents the process of OA [4]. For knee osteoarthritis (KOA), the use of hyaluronan as a visco-supplementation is a well-known option. Hyaluronan is known to boost viscoelasticity of synovial fluid and reduced pain [5]. It has pharmacological actions such as analgesic [6], anabolic [7], anti-inflammatory [6], and antinociceptive action [5]. Endogenous hyaluronan synthesis is also promoted by stimulation of CD44 receptor binding [7]. However, the use of hyaluronan in KOA continues to be debated [5–8]. Most findings suggest a significant effect-to-good-effect [9–11]. A few studies have reported insignificant benefits of hyaluronan compared to placebos [12]. Several guidelines suggest hyaluronan injection for KOA [13].

At present, several hyaluronan preparations are available that have different dosage forms, origins, and concentrations. In most of the formulations, hyaluronan is derived from rooster comb tissue, and dosing schedules are typically 3, 4, or 5 intra-articular injections [5]. However, single hyaluronan injections have been reported associated with patient convenience, safety, and effectiveness [14]. For such scenarios, chemically cross-linked hyaluronan (CCH) and avian derived hyaluronan (ADH) injections could be prepared to have competitive activities and single dose regimen [5].

The primary aim of the study was to decrease knee pain by intra-articular hyaluronan injections in KOA patients. The secondary outcome of the work was to compare tolerability and efficacy of CCH and ADH injections.

## Material and Methods

### Materials

CCH (HYA-JOINT Plus) was purchased from SciVision Biotech, Taiwan. ADH (Hylan G-F 20) was purchased from Sanofi-Aventis, Pharma Beijing Co., Ltd., China.

### Ethical consideration and consent to participate

The study was registered in the Research Registry (<https://www.researchregistry.com/>), UID No.: researchregistry3500, dated November 21, 2015. The study was approved by the Review

Board of the First Affiliated Hospital of Xiamen University, China. The protocol for the study (PR/CL/Re/16/81, dated November 15, 2015) was maintained under the law of PR China, CONSORT guidelines, and 2013 Declarations of Helsinki. All enrolled patients signed an informed consent regarding interventions, pathology, and publications of the study in all forms (electronic and hard) irrespective of time, place, and language, before the interventions.

### Design of the study

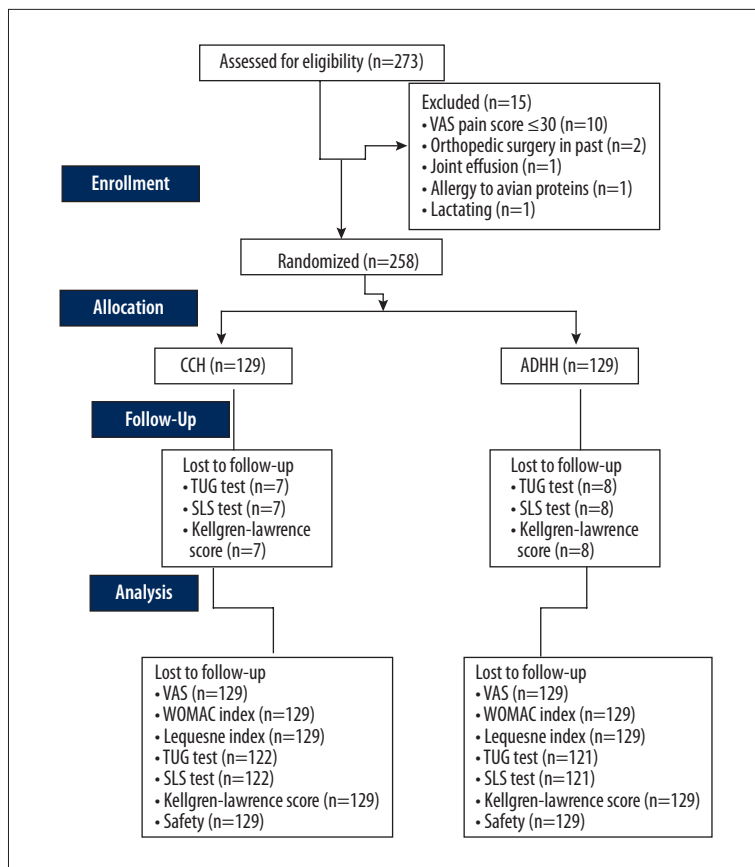
In total, 258 patients were included in study using simple randomization (1: 1 ratio, computer generated), parallel, double-blind (patient and consultant blind) study with a 6-month follow-up period. OpenEpi 3.01-English (Epidemiologic Statistics for Public Health, USA) software was used for prior sample size calculation, which was found to be 129. The confidence limit was 95%. Population size (N) was 258, hypothesized percentage frequency of N was  $79 \pm 5\%$ , confidence limits was 5%, design effect for cluster surveys was 1. CONSORT flow diagram of the study is presented in Figure 1. Sequentially numbered randomization was performed by authors.

### Inclusion criteria

All patients admitted to the Department of Orthopedics, the First Affiliated Hospital of Xiamen University, Xiamen, China, who had KOA for more than 180 days (confirmed by radiography) for treatment purposes from December 1, 2016 to June 30, 2017 were included in the study. Patients who were older than 38 years of age and younger than 80 years of age were included in the study. Patients who had an average visual analog scale (VAS) pain score of more than 30 were included in the study. Patients who had a Kellgren-Lawrence score of 2 or 3 were included in the study. The demographic characteristics of enrolled patients at the time of enrollment (baseline; BL) are represented in Table 1. The enrolled patients had no significant differences regarding demographic characteristics ( $P > 0.01$ ).

### Exclusion criteria

Patients who had average VAS pain scores of 30 or less were excluded from the study. Patients who had encountered lower limb, spine, or any orthopedic surgery in the past 10-years were excluded from the final enrollment. Patients who had apparent joint effusion or remarkable knee instability or deformity were excluded from the study. Patients who had an allergy to avian proteins, were lactating, or were pregnant were excluded from the study. Patients who had received intra-articular injections to the knee for KOA within the last 6 months were excluded. Patients who had neoplasm, rheumatoid arthritis, hemiparesis, or active infection were excluded from the final enrollment. Patients who had Kellgren-Lawrence score of 1 were excluded from the study.



**Figure 1.** A Randomized, double-blind trial chart. The population size (N) was 258, the confidence level was 95%; the hypothesized percentage frequency of N was 79±5%, the confidence limit was 5%, and the design effect for cluster surveys was 1. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; TUG, Timed “Up-and-Go”; SLS, single-limb stance; VAS, visual analog scale.

**Interventions**

Patients received a single intra-articular injection of CCH (60 mg/3 mL), the CCH group, or ADH (60 mg/6 mL) the ADH group. All injections were made using 1.5 inch and 21-gauge needle by well-trained nursing staff who were clinically involved in the research and blinded for the study. No painkiller was taken by the patients during enrollment and follow-up. Paracetamol was the only rescued drug allowed for pain [5]. All hyaluronan injections were performed under the guidance of a physiatrist who had more than 10 years of experience. The area of the skin of the targeted knee was prepared and the ultrasound (Accuvix XQ; Samsung Medison Co., Ltd., Korea) probe was put near the puncture side and the injection were made as guided by ultrasound and color jet. If the injection failed as an intra-articular injection, then the patient was reinjected with hyaluronan as per the guidance of a consultant [15].

**Radiographic Kellgren-Lawrence score**

Radiographic Kellgren-Lawrence score was detected by magnetic resonance imaging (MRI) at baseline and after 6 months of treatment. The MRI-based grading was as follows: grade 1 was doubtful narrowing of the joint space with possible osteophyte formation, grade 2 was possible narrowing of the joint

space with definite osteophyte formation, and grade 3 was definite narrowing of joint space, moderate osteophyte formation, some sclerosis, and possible deformity of bony ends [16].

**Knee pain measurement**

The primary aim of the study was to decrease knee pain. The pain was measured in each enrolled patient by VAS score at baseline and at 1 month, 3 months, and 6 months of follow-up. In the VAS score, a value of zero was indicated if there was no reported pain and a value of 100 was indicated for the worst possible pain [17].

**Secondary outcomes: the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, Likert scale)**

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, Likert scale) is a questionnaire with 24 questions. It included 3 subscales for stiffness, physical function, and pain. The value of zero indicated a good condition and the value of 96 indicated the worst possible outcome [18].

**Lequesne index score**

The Lequesne index score was included as a measure of a prior week evaluation of activities of daily living, walking distance,

and pain. The value of zero indicated normal function and the value of 24 indicated worst possible function [19].

### Timed “Up-and-Go” (TUG) test

The Timed “Up-and-Go” (TUG) test was defined as the time for the patient to rise from a chair, walk 3 meters, turn around, walk back, and sit down in the chair [20].

### Single-limb stance (SLS) test

The single-limb stance (SLS) test was defined as the time for the patient to raise the targeted foot without touching one’s low-er extremity and maintaining balance as long as possible [10].

### Patient satisfaction

Patient satisfaction was defined by use of a simple questionnaire. The satisfaction was graded between zero to 100. Zero was considered completely dissatisfied and 100 was considered completely satisfied [10].

### Safety assessment

Safety assessment was assessed on adverse events including joint pain, joint swelling, joint stiffness, joint effusion, limb weakness, injection site paresthesia, back pain, and infection as reported during follow-up. The decision to consider an event as an adverse event was based on the decision of evaluator(s) (nursing staff). Any dispute of a decision was resolved by a discussion with other evaluators [5,11]. A total of 15 evaluators were involved in the present study, including the physiatrist who conducted the injections and the investigator who conducted the assessments.

### Statistical analysis

InStat (GraphPad, USA) was used for the statistical analysis. Chi-squared test for independence was performed between demographical characteristics of enrolled patients between groups at baseline and for a radiographic Kellgren-Lawrence score between baseline and after 6 months of treatment. The Wilcoxon test following Bonferroni adjustment was performed for VAS analog, WOMAC score, Lequesne Index score, TUG test, and SLS test between baseline and after 1 month, 3 months, and 6 months follow-up [21]. Independent *t*-test [22] following Bonferroni adjustment [21] was performed for VAS analog, WOMAC score, Lequesne Index score, patient satisfaction, and adverse effects between groups at 1-month, 3-months, and 6-months follow-up. The Mann-Whitney U test following Bonferroni adjustment was performed for the TUG test and the SLS test between the groups at 6-month follow-up [21]. Results regarding drug actions were considered significant at

95% confidence level and demographic characters were considered significant at 99% confidence level.

## Results

There were 3 cases of intra-articular injection failure. In such conditions, hyaluronan was reinjected. Fifteen patients were not available for the follow-up study. They were contacted by telephone, email, or other social media and their data were collected for statistical analysis. CCH injections decreased the VAS pain score (Table 2) and total WOMAC score (Table 3) more strongly than that of ADH injections. Moreover, CCH injections strongly decreased the Lequesne index score during follow-up compared to ADH injections (Table 4). Radiographic Kellgren-Lawrence score grading is shown in Figure 2. Both the CCH group and the ADH group had the same kind improvement in Kellgren-Lawrence score after 6-months (Table 5).

Since 15 (7 from the CCH group and 8 from the ADH group) were not available for follow-up study, the TUG and SLS data were not evaluated for these cases. However, there was no significant difference between TUG and SLS time at baseline between the 2 groups. After 6 months of follow-up, patients who received ADH injections had improved TUG test times ( $P=0.0148$ ,  $q=3.385$ ) as compared to baseline (Figure 3).

After 6 months of follow-up, patients who received CCH injections had improved SLS times ( $P<0.0001$ ,  $q=8.76$ ) compared to patients who received ADH (Figure 4).

Both groups of patients had equal patient satisfaction (Table 6) after 1 month, 3 months, and 6 months.

Treatment-emergent adverse effects were the same in both groups after 6 months of follow-up ( $P\geq 0.05$  or/and  $q\leq 2.4$  1, Figure 5).

## Discussion

Visco-supplement has been reported as an effective treatment for KOA [13]. This study compared 2 different ultrasound-guided hyaluronan injections in KOA patients. There are different visco-supplements used to treat KOA that differ according to the nature of origin and molecular weight [23,24]. This study provided data to inform the choice of hyaluronan injection in KOA.

After 6 months of follow-up, the WOMAC pain score was improved:  $43.32\pm 7.9\%$  in the CCH group and  $42.96\pm 8.46\%$  in the ADH group as compared to baseline. The threshold of the WOMAC pain score in case of OA, as accepted for clinical importance, is 12–18% [5,25]. In consideration of our study results

**Table 1.** The demographic characteristics of patients at the time of enrolment.

Characteristics		Groups		Comparisons
		CCH	ADH	
Sample size		129	129	p-Value
Age (year)		64.82±9.23	62.02±11.25	0.579
Gender	Male	30 (23)	35 (27)	0.566
	Female	99 (77)	94 (73)	
Site of KOA	Left	61 (47)	70 (54)	0.319
	Right	68 (53)	59 (46)	
BMI (kg/m <sup>2</sup> )		27.44±2.4	27.62±2.31	0.927
Duration of KOA (year)	<5	85 (66)	81 (63)	0.417
	5≥ but 10<	35 (27)	37 (29)	
	≥10	9 (7)	11 (8)	
Marital status	Married	121 (94)	125 (97)	0.376
	Unmarried	8 (6)	4 (3)	
Ethnicity	Chinese	127 (98)	128 (99)	0.5
	Non-Chines	2 (2)	1 (1)	
TUG (sec)		12.66±1.53	12.71±1.61	0.88
SLS (sec)		18.71±1.5	18.20±1.49	0.971

KOA – knee osteoarthritis. Continuous data were represented as mean ±SD and constant data were represented as a number (percentage). BMI – body mass index. *Chi-squared* Test for Independence was used for statistical analysis. A p<0.01 was considered as significant. N/A – not applicable; TUG – timed “Up-and-Go”; SLA – single-limb stance test.

**Table 2.** Comparison of Visual analog scale pain score.

Type of hyaluronan injections	Sample size	Groups		Comparisons between group	
		129	129	p-Value	q-Value
		Chemically cross-linked	Avian derived		
VAS	CCH	ADH			
BL		58.82±1.4	58.58±1.49	0.876	N/A
30 days	Pain score	24.22±1.43	35.47±2.87	<0.0001	46.216
	p-Value	<0.0001	<0.0001		
	q-Value	170.35	89.051		
90 days	Pain score	23.45±1.67	35.02±1.89	<0.0001	56.178
	p-Value	<0.0001	<0.0001		
	q-Value	174.17	90.733		
180 days	Pain score	21.6±2.14	34.33±1.96	<0.0001	54.803
	p-Value	<0.0001	<0.0001		
	q-Value	183.29	93.39		

VAS – visual analog scale; BL – baseline. Data were represented as mean ±SD. Wilcoxon test (within the group) or independent *t*-test (between group) following Bonferroni adjustment was used for statistical analysis. A p<0.05 and q>2.652 were considered as significant. Within-group p-value was respect to BL. A 0: No pain and 100: Worst possible pain. N/A – not applicable.

**Table 3.** Comparison of the Western Ontario and McMaster Universities Osteoarthritis Index.

Sample size		Groups		Comparisons between groups	
		129	129		
Type of hyaluronan injections		Chemically cross-linked	Avian derived	p-Value	q-Value
WOMAC index		CCH	ADH		
<b>Pain score (0–20)</b>					
BL		10.5±0.97	10.46±1.01	0.7936	N/A
30 days	Pain score	6.29±0.45	6.33±0.51	0.0575	N/A
	p-Value	<0.0001	<0.0001		
	q-Value	49.676	45.588		
90 days	Pain score	6.23±0.52	6.26±0.53	0.1807	N/A
	p-Value	<0.0001	<0.0001		
	q-Value	50.317	46.455		
180 days	Pain score	5.9±0.61	5.91±0.64	0.6565	N/A
	p-Value	<0.0001	<0.0001		
	q-Value	54.251	50.301		
<b>Stiffness score (0–8)</b>					
BL		3.01±0.6	63.02±0.59	0.851	N/A
30 days	Score	2.31±0.46	2.31±0.47	1.102	N/A
	p-Value	<0.0001	<0.0001		
	q-Value	13.315	13.63		
90 days	Score	2.16±0.36	2.08±0.27	0.0677	N/A
	p-Value	<0.0001	<0.0001		
	q-Value	16.274	18.075		
180 days	Score	1.92±0.27	1.92±0.26	1.103	N/A
	p-Value	<0.0001	<0.0001		
	q-Value	20.712	21.038		
<b>Physical function score (0–68)</b>					
BL		35.89±2.53	35.98±2.55	0.7479	N/A
30 days	Score	25.7±1.5	27.57±0.96	<0.0001	8.364
	p-Value	<0.0001	<0.0001		
	q-Value	59.324	44.606		
90 days	Score	25.27±1.24	26.67±0.95	<0.0001	6.629
	p-Value	<0.0001	<0.0001		
	q-Value	61.805	49.303		
180 days	Score	24.69±1.11	25.67±0.95	<0.0001	4.758
	p-Value	<0.0001	<0.0001		
	q-Value	65.189	54.628		

**Table 3 continued.** Comparison of the Western Ontario and McMaster Universities Osteoarthritis Index.

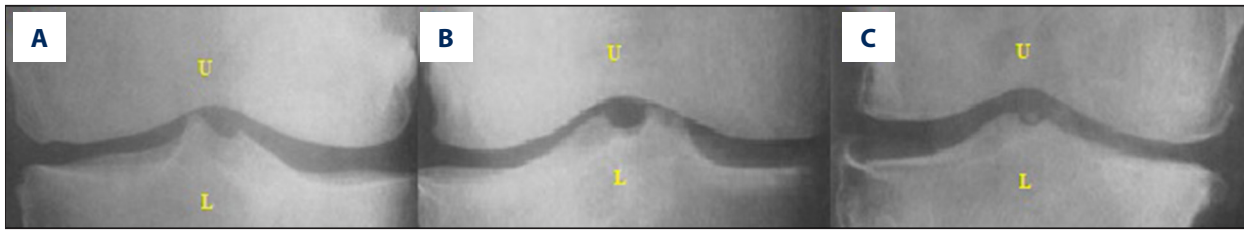
Sample size		Groups		Comparisons between groups	
		129	129	p-Value	q-Value
Type of hyaluronan injections		Chemically cross-linked	Avian derived		
WOMAC index		CCH	ADH		
Total score (0–96)					
BL		49.5±2.54	49.67±2.7	0.8345	N/A
30 days	Score	34.29±1.64	36.21±1.22		
	p-Value	<0.0001	<0.0001	<0.0001	8.11
	q-Value	78.999	66.973		
90 days	Score	33.66±1.42	35.01±1.15		
	p-Value	<0.0001	<0.0001	<0.0001	6.237
	q-Value	82.324	77.044		
180 days	Score	32.51±1.3	33.50±1.19		
	p-Value	<0.0001	<0.0001	<0.0001	4.753
	q-Value	88.326	80.642		

Data were represented as mean ±SD. Wilcoxon test (within the group) or independent t-test (between group) following Bonferroni adjustment was used for statistical analysis. A p<0.05 and q>2.652 were considered as significant. Within-group p-value was respect to BL. BL – baseline, N/A – not applicable. WOMAC – The Western Ontario and McMaster Universities Osteoarthritis Index (Likert scale). A 0: Good condition and 96: The worst possible outcome.

**Table 4.** Comparison of Lequesne Index Score.

Sample size		Groups		Comparisons	
		129	129	p-Value	q-Value
Type of hyaluronan injections		Chemically cross-linked	Avian derived		
Lequesne Index		CCH	ADH		
BL		11.13±1.96	11.21±2.04	0.7569	N/A
30 days	Pain score	8.04±0.58	8.91±1.13		
	p-Value	<0.0001	<0.0001	<0.0001	3.072
	q-Value	21.213	16.471		
90 days	Pain score	8.13±0.34	8.81±0.9		
	p-Value	<0.0001	17.194	<0.0001	4.354
	q-Value	23.322	<0.0001		
180 days	Pain score	7.88±0.35	8.37±0.73		
	p-Value	<0.0001	<0.0001	<0.0001	3.208
	q-Value	25.25	20.366		

VAS – visual analog scale. Data were represented as mean ±SD. Wilcoxon test (within the group) or independent t-test (between group) following Bonferroni adjustment was used for statistical analysis. A p<0.05 and q>2.652 were considered as significant. Within-group p-value was respect to BL. BL – baseline; N/A – not applicable. A 0: Normal function and 24: The worst possible function.

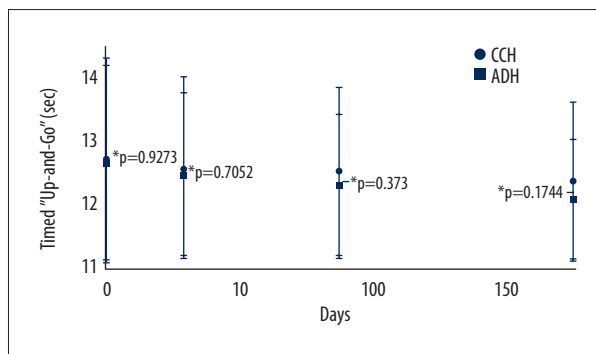


**Figure 2.** Radiographic for Kellgren-Lawrence score grading (magnetic resonance imaging): (A) Grade 1; (B) Grade 2; (C) Grade 3. U – upper portion of the knee, L – lower portion of the knee.

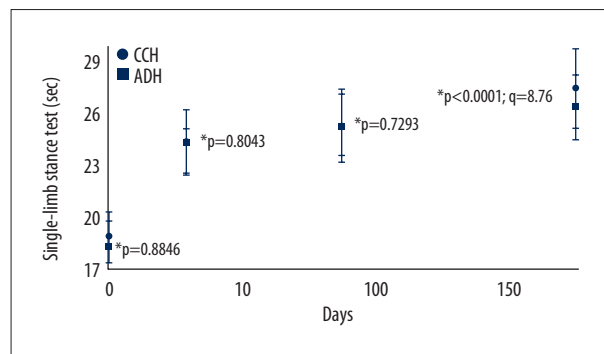
**Table 5.** Comparisons of radiographic Kellgren-Lawrence score.

Characteristics	Groups								
	CCH			ADH			Comparisons between CCH and ADH		
Level	BL	EL	Comparisons between BL and EL	BL	EL	Comparisons between BL and EL	BL	EL	
Sample size	129	122	p-Value	129	121	p-Value	p-Value	p-Value	
Radiographic Kellgren-Lawrence score	1	0 (0)	35 (29)		0 (0)	38 (31)			
	2	83 (64)	54 (44)	<0.0001	72 (56)	51 (42)	<0.0001	0.204	0.799
	3	46 (36)	33 (27)		57 (44)	33 (27)			

Chi-squared Test for Independence was used for statistical analysis. A  $p < 0.05$  was considered as significant. BL – baseline; EL – after six-months.



**Figure 3.** Timed "Up-and-Go" test. Data are represented as mean  $\pm$ SD; n=122 for the CCH group and n=121 for the ADH group. Timed "Up-and-Go" was low in the ADH group after 6 months of follow-up as compared to baseline (BL) ( $P=0.0148$ ,  $q=3.385$ ). The Wilcoxon test (within the group) or the Mann-Whitney U test (between group) following Bonferroni adjustment was used for statistical analysis.  $P < 0.05$  and  $q > 2.652$  were considered significant. Within group  $P$ -value was with respect to BL. CCH – chemically cross-linked hyaluronan injections; ADH – avian derived hyaluronan injections.



**Figure 4.** Single-limb stance test. Data are represented as mean  $\pm$ SD; n=122 for the CCH group and n=121 for the ADH group. Single-limb stance time was higher in the CCH group than the ADH group after 6 months of follow-up ( $P < 0.0001$ ,  $q=8.76$ ). The Wilcoxon test (within the group) or the Mann-Whitney U test (between group) following Bonferroni adjustment was used for statistical analysis.  $P < 0.05$  and  $q > 2.652$  were considered significant. Within group  $P$ -value was with respect to BL. CCH – chemically cross-linked hyaluronan injections; ADH – avian derived hyaluronan injections; BL – baseline.



Table 6. Patients' satisfaction.

Sample size	Group		Comparisons between groups
	129	129	
	Type of hyaluronan injections	Chemically cross-linked	
Period	CCH	ADH	p-Value
One month	59.68±2.44	59.55±2.28	0.7028
Three months	60.67±2.40	60.55±2.27	0.7352
Six months	61.67±2.41	61.54±2.29	0.7189

Independent *t*-test was used for statistical analysis. A  $p < 0.05$  was considered as significant. Missing data were collected via electronic conversation. Data were represented as mean ±SD. A 0: Completely dissatisfied and 100: Completely satisfied.

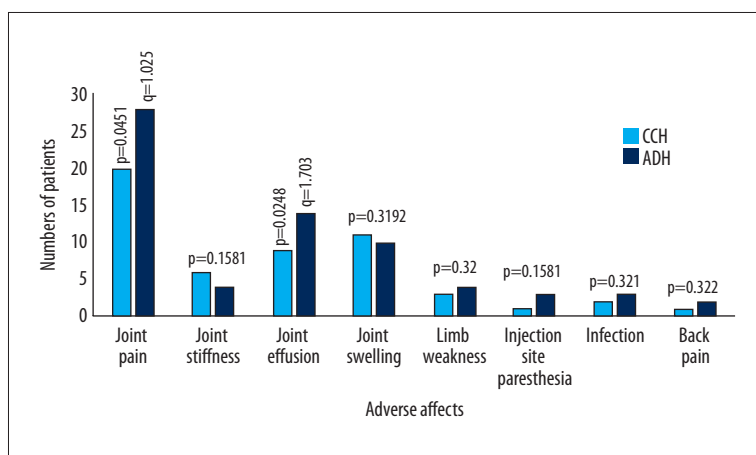


Figure 5. Treatment-emergent adverse effects after 6 months of follow-up. For statistical analysis, the adverse event was considered as 1 and the absent of that was considered as 0. Independent *t*-test following Bonferroni adjustment was used for statistical analysis. A  $P < 0.05$  and  $q > 2.41$  were considered as significant. Missing data were collected via electronic conversation. CCH – chemically cross-linked hyaluronan injections; ADH – avian derived hyaluronan injections.

for the WOMAC index, these findings were consistent with other available clinical trials on KOA.

At the end of the 6 months, the Lequesne index score was improved in the range of 13.77–40.21% for CCH group and 8.12–37.71% for ADH group as compared to baseline. For the effective form of the treatment, the threshold of the Lequesne index score is 30–40% in OKA [5,26]. The data on the Lequesne index in this study meet the requirement of therapy in OKA patients.

There was an improvement in TUG time in patients who received ADH injections at the end of 6 months compared to baseline. This was likely because of the excessive capsular distension effect of ADH on physical activity of patients [5]. There was an improvement in SLS time in patients who received CCH injections at the end of 6 months compared to those who received ADH injections. This was likely because of the efficacy of CCH injections in preventing catabolism of cartilage [27]. Further study is recommended to reveal the mechanism of actions for this finding.

Both types of hyaluronan injections had no reported harmful adverse effects. Our study data were in line with available

studies on different types of hyaluronan injections in KOA [5,6,14,28]. However, consideration should also include acute side effects like joint pain, joint swelling, and joint stiffness due to hyaluronan injection, the carrier of hyaluronan, the nature of origin, the injection technique(s) or the person who is administering the injection [5]. Further study is required to determine the cause of adverse effects.

To the best of our knowledge, there have been 2 studies that have compared different types of intra-articular hyaluronan injection in KOA patients. Both of these studies had follow-up periods of 26 weeks, but they had smaller sample size, did not use ultrasound guided intra-articular injections, and had no radiographic Kellgren-Lawrence score assessments [23,29]. It is a waste of resources if a study is carried out with a small sample size [30] and ultrasound is needed as a supportive tool in intra-articular injections [15]. The sample size and injection procedure in this study were chosen to prove the study hypothesis.

There were several limitations to our study. For example, the placebo-effect has been reported in KOA cases [12] but our study did not compare interventions with a placebo-control. In addition, oscillation of dose could affect therapeutic effect

of hyaluronan injection [5]. However, the volume of the administered drug (but the same equivalent dose) of hyaluronan injection in the 2 groups was different. In addition, the cost of the treatment between the 2 groups was not compared.

## Conclusions

This is the first study to look at the origin and efficacy of different hyaluronan injections in KOA cases. We demonstrated that CCH injection was superior to ADH injection in several ways. This suggests that formulations that consider the origin of the hyaluronan, and the characteristics of patients could

be beneficial for effective KOA therapy. Further studies are required to evaluate the different effects based on the origin of hyaluronan with regards to different characteristics of patients.

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## Conflict of Interest

None.

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