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Hyaluronate improves pain, physical function and balance in the geriatric osteoarthritic knee: a 6-month follow-up study using clinical tests[1]

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Summary

Objective: To investigate the effects of intraarticular hyaluronic acid (HA) (Artzal, Seikagaku Corp., Japan) in geriatric participants with unilateral knee osteoarthritis (OA).

Method: This was a prospective, observer-blind study with 6 months follow-up done in the setting of an outpatient rehabilitation department in a university-affiliated tertiary care medical center. Sixty-eight patients, aged 65 years or above, with symptoms and radiographic evidence of unilateral knee OA for at least 6 months were recruited. Patients received five weekly intraarticular injections of Artzal into symptomatic knees. Fifty-six participants completed the study. Fifty age-, body mass- and gender-matched healthy individuals were selected as control. Visual analog scale (VAS), Lequesne index and four balance tests including single-leg stance test (SLS), function reach test (FRT), timed "Up-and-Go" test (TUG) and Berg balance scale (BBS) were assessed before injection and at each follow-up visit in the OA group. Four balance tests were obtained on healthy participants for data comparison.

Results: Before Artzal injections, the OA group showed significantly worse VAS, Lequesne index and four balance tests scores than did the control group ($P < 0.001$). Significant improvement in all outcome measures were noted at 1 week, 1, 3 and 6 months post the fifth injection compared with baseline before injection. Local adverse events were reported in four patients (7.1%).

Conclusion: Significant improvement in pain, physical function and balance tests was demonstrated after five weekly Artzal injections in geriatric patients with knee OA. The effect had rapid onset at 1 week and may last for 6 months.

Key words: Balance, Knee osteoarthritis, Hyaluronic acid, Viscosupplementation.

Introduction

Osteoarthritis (OA) of the knee is a common chronic degenerative disorder, affecting 30–40% of the population by the age of 65 years[1]. It is a major cause of locomotor disability among the elderly[2,3] and has been implicated as a risk factor for falls in older adults[4]. Current treatment options for knee OA include the use of simple analgesics or nonsteroidal antiinflammatory drugs (NSAIDs), glucosamine and chondroitine sulphate, intraarticular corticosteroid injections, physical therapy, weight reduction, orthotics and surgical treatment ranging from arthroscopy to total knee replacement[5]. Since there is no curative therapy for OA, the most pressing need for the majority of patients with OA is nonoperative care that helps to relieve symptoms and improve function[6].

Intraarticular hyaluronic acid (HA) is a relatively new option for improving pain and articular function and has gained popularity in the treatment of knee OA. Several trials have attempted to evaluate the effect of intraarticular HA in OA of the knee[7–15]. Conflicting conclusions regarding efficacy have been observed among studies and it is not clear from these studies whether elderly populations respond well to HA therapy. In addition, no study to date has assessed whether balance function would change in geriatric OA individuals after HA injections.

Balance impairments are associated with an increased risk of falls and poorer mobility measures in the elderly population[16]. The presence of knee OA may accelerate the deterioration of balance control systems or compound the effects of aging. However, studies that evaluated balance in people with knee OA are limited[17–19]. Hassan *et al.*[18] and Wegener *et al.*[19] demonstrated increased postural sway in subjects with knee OA when standing on a firm surface in both AP and lateral directions. In contrast, Hurley *et al.*[17] were unable to detect a deficit in body sway in individuals with OA, despite the OA group being more unsteady

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when compared with controls. All these studies have utilized force platforms. However, these expensive apparatus are not readily available to the majority of clinicians in the clinical setting. Furthermore, falls and loss of balance most commonly occur during dynamic tasks such as walking. It is therefore important that the evaluation of balance incorporates testing procedures that reflect the dynamic nature of locomotor tasks[20,21]. In this study, simple, inexpensive and easy-to-administer clinical tests were used to assess both static and dynamic balance.

The purpose of this study was to determine the efficacy of five weekly intraarticular injections of HA in geriatric participants with unilateral knee OA. Pain as documented via visual analog scale (VAS), functional parameters including Lequesne index, and clinical tests of balance by using four simple and easy measures were evaluated.

Methods

PARTICIPANTS

The study was approved by the institutional review board for human investigation and all subjects provided signed informed consent before being enrolled in the study. Participants were divided into two groups: those with OA and the non-OA healthy control. The group with OA consisted of 68 participants, aged 65 and older, with unilateral symptomatic knee OA for at least 6 months. Fifty age-, body mass- and gender-matched healthy individuals without knee OA were selected as the control group. Subjects with a history of arthritis, major trauma to the lower limbs, history of prolonged knee pain in the past year, or displaying abnormality on physical examination of the knee (effusion, palpable warmth, ligamentous laxity, etc.) were excluded from the control group. X-rays of bilateral knees were performed to exclude asymptomatic knee OA according to the Ahlbäck grading system[22].

The inclusion criteria for the group with OA included unilateral knee pain with no improvement after conservative treatment for at least 6 months, average pain on knee movement of at least 3 cm on a 10-cm VAS at the time of inclusion, grade I or II tibiofemoral OA of the knee according to the Ahlbäck grading system based on weight-bearing anteroposterior and lateral knee radiographs taken within the previous 6 months[22] (grade I = joint space narrowing <3 mm; grade II = joint space obliterated or almost obliterated). Knee radiographs were reviewed by one of the authors.

Exclusion criteria included previous orthopedic surgery on the spine or lower limbs, knee instability or marked deformity on examination, intraarticular steroid or HA injection within the past 6 months, history of rheumatoid arthritis, gout, recurrent pseudogout or any other inflammatory arthropathy, and presence of severe neurological, cardiac, psychiatric disorders or other specific conditions (neoplasm, diabetes mellitus, recent trauma, severe dizziness, visual deficit, etc.) that would interfere with the clinical assessment during the study period.

OUTCOME MEASURES

The patient rated the intensity of pain with regard to average pain on knee movement over the previous week using a 10-cm horizontal VAS[23]. The VAS was marked in 1-cm increments with the descriptors "no pain" and "worst pain" at either end. Subsequent recordings of VAS were done on separate sheets of paper. This prevented the subjects from comparing the present VAS with the previous one.

Lequesne index was used to assess severity of knee symptoms during the last week[24]. It is validated and includes the measurement of pain (5 items), walking distance (2 items), and activities of daily living (4 items). Maximal score is 24 and higher scores represent worse function.

Single-leg stance test (SLS) is done by raising one foot up without touching it to the supported lower extremity with knee OA and maintain balance for as long as possible. Failure occurs if the stance foot shifts in any way or the non-stance foot touches the ground. In our study, each participant performed three trials, and the best result of the three trials was recorded[25]. SLS time of <30 s in an older ambulatory outpatient population is associated with a higher risk of falling[26].

The functional reach test (FRT) is used to screen for balance abilities[27]. The test evaluates how far a participant can reach forward beyond arm's length while maintaining a fixed base of support in the standing position. Three measurements were obtained in our study, and an average of the three measurements was taken as the final measurement. Validity of data for the FRT was demonstrated by a significant correlation ($r = 0.71$) with laboratory center of pressure measurements in a study of 128 people (aged 21–87 years)[27]. Functional reach is a measure of the anterior limit of stability. A longer functional reach suggests that participants have a larger anterior margin of stability, hence better dynamic balance control.

Timed "Up-and-Go" test (TUG) is a simple test of basic physical functional mobility for frail elderly persons with high interrater reliability and content reliability[28]. A patient is asked to rise from an armchair, walk 3 m at a safe and comfortable pace, turn around, walk back to the chair, and sit down again. The whole procedure is demonstrated first before the actual test. The score is the time in seconds it takes to complete these tasks. It also predicts whether a patient can walk safely alone outside[28].

Berg balance scale (BBS) is a 56-point scale to evaluate performance during 14 common activities, such as standing, turning, and reaching for an object on the floor. The BBS examines static and dynamic balance with progressing difficulty from sitting to single-leg standing. Higher scores correspond to better balance. It has high interrater and intrarater reliability. Although it is designed to be used as a clinical assessment tool, scores on the BBS have been shown to correlate with laboratory tests of balance[29].

STUDY DESIGN

This was a prospective, observer-blind controlled study designed to examine the efficacy of intraarticular HA on reported pain, functional ability and clinical balance tests in elderly individuals with unilateral OA of the knee.

Baseline characteristics (age, sex, weight, height and body mass index) were recorded in all participants. Before the first injection, participants in the OA group completed baseline measures including VAS, the Lequesne index, and four balance tests including SLS, FRT, TUG and BBS. The control group also completed four balance tests for data comparison. SLS and TUG tests were measured on a stopwatch to the nearest 1/100 of a second. The order of testing was as follows: SLS, FRT, TUG and BBS with 3 min rest between each test.

The OA patients were given five weekly intraarticular injections of HA (Artzal, 2.5 ml injection, 1% hyaluronan, average molecular weight 900 kDa) by the same physician

using aseptic procedures. If an effusion was present, it was aspirated before injecting. Follow-up assessments were made at intervals of 1 week, 1, 3 and 6 months after the fifth injection. The different physician who was responsible for the evaluation of the participants remained unaware of each participant's group and treatment throughout the entire study. Patients taking analgesics or NSAIDs stopped them at least 7 days prior to the first assessment. During the study period, no regular analgesics, NSAIDs or physical therapy for knee joint conditions were permitted. Acetaminophen (500 mg), up to 4 g/day was allowed as rescue medication. If the treatment dose was above the stipulated limit (acetaminophen 4 g/day), the patient was regarded as a clinical failure. The administration of all analgesic medication during the study period was recorded on a diary card by the patient.

To monitor the safety of each injection, the occurrence of systemic and local adverse events, defined as any unwanted events whether it was thought to be related to the study drugs or not, were recorded.

STATISTICAL ANALYSIS

All statistical procedures were conducted with the Statistical Package for the Social Sciences (version 12.0; SPSS Inc., Chicago, Illinois). The data were presented as mean ± standard deviation and independent *t*-tests were used to compare differences between the OA group and the control group. Baseline characteristic of sex was compared using the chi-square test. Change of outcome measures in VAS, Lequesne index, FRT, TUG and BBS were assessed using paired *t*-test comparing baseline value with each follow-up score. Changes in SLS were analyzed using Wilcoxon signed rank test. *P* values of less than 0.05 were regarded as significant.

Results

Sixty-eight geriatric OA patients were recruited in the study. Five patients withdrew from the study before the final injection (two moving to another city and three because of traffic accident and unrelated intercurrent illness). Seven patients were lost to follow-up because of noncompliance and missing the scheduled appointments. Fixty-six OA participants (21 females, 35 males) with an average age of 74.7 ± 5.4 years (range 65–84 years) completed the study. Fifty healthy participants (19 females, 31 males) with an average age of 73.8 ± 5.5 years (range 65–83 years) were selected as the control group. Baseline characteristics of all participants are presented in Table I. Groups were not different in age, sex, weight, height and body mass index.

Table II provides a summary of outcome measures. The group with knee OA before Artzal injections showed significant worse scores in SLS, FRT, TUG and BBS than did the control group ($P < 0.001$). Compared with baseline findings, results of VAS, Lequesne index and four balance tests improved significantly in all of our OA patients after the completion of five weekly injections. These effects were rapid at 1 week after the fifth injection, and the treatment effects could last for at least 6 months.

Mean values of differences between baseline and postinjection follow-up scores at each time point are shown in Table III. The mean VAS value reduced from 5.4 ± 2.4 cm at baseline to 3.1 ± 1.7 cm at 1 week after the fifth injection (mean reduction = 2.3 cm) ($P < 0.001$) (Table II). The mean reduction was 2.8 cm at 1 month and 3.0 cm at 3 months.

Table I
Baseline characteristics of all participants

Characteristics	Knee OA group ($n = 56$)	Control group ($n = 50$)	*P* value
Age (years)	74.7 ± 5.4	73.8 ± 5.5	0.503
Sex (F/M)	21/35	19/31	0.800
Weight (kg)	68.2 ± 8.8	67.4 ± 8.2	0.699
Height (cm)	158.3 ± 5.6	157.9 ± 5.9	0.743
BMI (kg/m^2)	27.3 ± 4.1	27.2 ± 4.0	0.892
OA knee (Lt/Rt)	25/31		
Ahlbäck classification			
Grade I	26	0	
Grade II	30	0	
Disease duration (years)	5.3 ± 4.7		

Data are mean ± standard deviation; BMI = body mass index.

The reduction still remained significant at 6 months follow-up $P < 0.001$) (Table III). The Lequesne index score reduced from 10.3 ± 3.7 prior to injections to 7.2 ± 3.8 at 1 week after the fifth injection ($P < 0.001$). A considerable reduction to 5.9 ± 3.3 and 5.7 ± 3.5 were noted at 1 month and 3 months ($P < 0.001$ and $P < 0.001$, respectively, compared with baseline), and the benefit persisted up to 6 months ($P < 0.001$) (Table II). Treatment with intraarticular Artzal also improved balance function as assessed by SLS, FRT, TUG and BBS tests. Each result remained significantly better than baseline at the postinjection 1-week follow-up ($P < 0.001$ for each test) and the improvement also remained significant at 6 months follow-up ($P < 0.001$ for each test) (Table III).

Local adverse events with transient pain at injection site and local warmth and swelling with varying intensities were reported in four patients (7.1%). No severe or systemic adverse events were observed in the participants during the study.

OA patients who received intraarticular injections used much less analgesics. The demand for analgesics (acetaminophen) fell from an average of 14 tablets weekly at baseline to 4, 3, 3 and 3 tablets weekly at 1 week, 1, 3 and 6 months postinjection, respectively ($P < 0.001$ compared with baseline) (Table II).

Discussion

The purpose of this study was to evaluate efficacy of intraarticular HA on reported pain, functional ability and clinical tests of balance in elderly individuals with unilateral OA of the knee.

Various studies with HA had also used the Lequesne index score to quantify joint function, while VAS had been proved to supply reliable data in the documentation of pain levels[23,24]. Pietrogrande and Turchetto[12] showed a pain reduction 60 days after the intraarticular injections of HA from VAS values of 6 cm down to 2 cm. According to a recent review, intraarticular injection of HA reduced knee pain in patients with OA by 20–40% over 6–12 months[13]. Di Marco and Letizia[14] analyzed pain on weight bearing following treatment with HA and they found a reduction of the pain level from 6.7 cm to 4.7 cm. It appeared that the described pain relief as in the previous studies was also documented in our study.

The functional analysis as defined by Lequesne in past studies with HA documented improved scores by about 4 points with a follow-up of 1 year[8,15]. Lequesne defined effective treatment forms as those leading to a score

Table II
Summary of outcomes before and after treatment

	OA knee group ($n = 56$)						Control group ($n = 50$)
	Baseline	1 week	1 month	3 months	6 months	*P* value	
VAS†	5.4 ± 2.4	3.1 ± 1.7	2.7 ± 1.5	2.4 ± 1.3	2.5 ± 1.5	AB* AC* AD* AE*	
Lequesne index†	10.3 ± 3.7	7.2 ± 3.8	5.9 ± 3.3	5.7 ± 3.5	5.7 ± 3.2	AB* AC* AD* AE*	
SLS	23.94 ± 41.40	34.1 ± 47.47	34.79 ± 47.34	38.18 ± 46.59	38.12 ± 46.60	AB* AC* AD* AE* AF*	50.42 ± 42.31
FRT	22.80 ± 4.78	25.60 ± 4.84	26.56 ± 4.77	25.56 ± 4.11	25.67 ± 4.42	AB* AC* AD^{+} AE* AF*	28.81 ± 4.31
TUG†	12.90 ± 5.01	11.04 ± 3.81	9.40 ± 2.46	9.19 ± 2.75	9.24 ± 2.60	AB* AC* AD* AE* AF*	9.14 ± 2.65
BBS	50.03 ± 5.38	52.25 ± 3.68	52.94 ± 3.08	53.14 ± 3.27	53.14 ± 3.01	AB* AC* AD* AE* AF*	53.20 ± 3.11
Acetaminophen (tablets/week)	14.3 ± 2.4	4.1 ± 2.3	3.4 ± 2.1	3.1 ± 2.3	3.3 ± 2.2	AB* AC* AD* AE*	

Note: Values are the mean ± standard deviation; VAS = visual analogue scale; SLS = single-leg stance test; FRT = function reach test; TUG = timed "Up-and-Go" test; BBS = Berg balance scale.

The possible range for the VAS score was 0–10; the possible range for the Lequesne index was 0–24; and the possible range for the BBS score was 0–56.

AB is the comparison for the OA group before and 1 week after the intraarticular hyaluronate injections; AC is the comparison for the OA group before and 1 month after the intraarticular hyaluronate injections; AD is the comparison for the OA group before and 3 months after the intraarticular hyaluronate injections; AE is the comparison for the OA group before and 6 months after the intraarticular hyaluronate injections; and AF is the comparison for the OA group before injection with control group.

*$P < 0.001$ vs baseline; $^{+}P = 0.001$ vs baseline.

†Higher scores represent worse pain or function.

improvement of 30–40% at the time of follow-up[30]. In our study, the reduction of the Lequesne index scores from 10.3 ± 3.7 points at baseline to 5.7 ± 3.2 points at 6 months follow-up represented an improvement of 44.7%, which was above the upper end of the values used to define treatment effectiveness. Therefore, using the Lequesne criteria, the intraarticular administration of HA can be defined as an effective therapeutic measure in the treatment of geriatric knee OA.

It is not clear whether elderly populations respond well to intraarticular HA. In a previous study by Lohmander *et al.*[8], a subgroup analysis suggested that patients aged 60 years or above with a baseline Lequesne index above 10 and radiographically verified OA of the knee (Ahlbäck grade I or II) showed significant benefit from intraarticular treatment with HA. The study by Wobig *et al.*[11] also showed improvement after HA treatment in patients over 60 years old. In a meta-analysis, patients older than 65 years of age and those with the most advanced radiographic stage of OA (complete loss of the joint space) were less likely to benefit from intraarticular injection of HA[31]. In our study, we demonstrated that patients older than 65 years of age with radiographically verified OA of the knee (Ahlbäck grade I or II) could benefit from intraarticular injections of HA.

To our knowledge, this was the first study that examined the effect of intraarticular injection of HA on balance. Poorer balance test scores were demonstrated in the geriatric OA participants compared with non-OA healthy participants by using simple clinical tests in our study. The close matching of control participants in our study supported that the observed balance deficits were due to the presence of knee OA, and not due to inherent differences between groups with regard to age, gender or body mass index. Significant improvement in clinical balance tests was shown in addition to pain reduction and improvement in physical function. These effects were rapid at 1 week and could last for at least 6 months.

Balance is an important component of performance for transfer, ambulatory tasks and many activities of daily living. Several potential mechanisms may be responsible for the balance deficits observed within the geriatric OA participants. Previous investigators have demonstrated that vision, peripheral proprioception and lower limb muscle strength appear to be important determinants of balance in the elderly[32,33]. Individuals with knee OA display reductions in quadriceps strength and activation as well as impairments in knee joint proprioception[17,34–37]. These deficits, in combination with the aging process, may culminate in greater impairments in balance in this elderly OA population, compared with their age-matched healthy counterparts. Pain associated with knee OA may also play a role in balance impairments. Messier *et al.*[38] reported that adults aged 65 years or older with chronic knee pain experienced significant declines in balance and lower extremity strength

Table III
Mean change from baseline in VAS, Lequesne index, SLS, FRT, TUG and BBS

	VAS†	Lequesne index†	SLS	FRT	TUG†	BBS
1 week	−2.3 ± 2.0*	−3.1 ± 2.1*	10.16 ± 16.99*	2.80 ± 3.90*	−1.87 ± 2.67*	2.2 ± 2.9*
1 month	−2.8 ± 1.8*	−4.4 ± 2.0*	10.84 ± 16.97*	3.75 ± 3.99*	−3.51 ± 3.12*	2.9 ± 3.4*
3 months	−3.0 ± 1.9*	−4.6 ± 1.5*	14.24 ± 19.46*	2.75 ± 4.53^{+}	−3.71 ± 3.18*	3.1 ± 2.8*
6 months	−2.9 ± 2.2*	−4.6 ± 2.1*	14.18 ± 20.26*	2.86 ± 4.28*	−3.66 ± 3.13*	3.1 ± 2.9*

VAS = visual analog scale; SLS = single-leg stance test; FRT = function reach test; TUG = timed "Up-and-Go" test; BBS = Berg balance scale. The possible range for the VAS score was 0–10; the possible range for the Lequesne index was 0–24; the possible range for the BBS score was 0–56.

*$P < 0.001$ vs baseline; $^{+}P = 0.001$ vs baseline.

†Higher scores represent worse pain or function.

over a 30-month period. Knee pain may limit activity and reduce knee extensor and flexor strength, which could compromise effective and timely motor responses in postural control[39]. Furthermore, pain may result in reduced loading of the affected joint[40], potentially jeopardizing an individual's ability to maintain their center of mass within the base of support. The mechanisms by which HA mediate its clinical benefit seem to be multifactorial and biologically related. More researches to study the impact of knee OA on balance and the effects of HA on the joint may allow possible mechanisms of disability in the OA population to be elucidated, and may permit more effective management of patients with this disease.

The study had several limitations. A limitation of this study included the absence of a control group. The placebo effects associated with joint injection were therefore not investigated. We did not make use of a saline control group since saline injection could not be excluded as a source of a noxious stimulus and it was inappropriate to subject these symptomatic OA patients to a placebo. The number of participants studied was small and they were not blinded in treatment. OA participants were recorded by age, gender, body weight and body mass index. They were not analyzed on the basis of severity of OA, preinjection or postinjection functional levels and assistive devices' usage. In future studies, we would like to recruit OA patients with a higher Ahlbäck scale grade (i.e., III–V), to see whether intraarticular HA injections can improve balance function in severely obliterated knee joints. The more precise identification of subgroups of patients who would most benefit from this treatment, as well as the role for repeated series of injections, must be clarified in the future. A longer, longitudinal study with a larger sample size is required to determine whether viscosupplementation could attenuate balance decline in the geriatric patients with knee OA and more researches are needed to investigate whether viscosupplementation can improve balance to a level that would substantially reduce fall risk.

Conclusion

On the basis of this prospective, single-blind controlled study of geriatric patients with unilateral knee OA (Ahlbäck grading scale of stages I and II), we concluded that five weekly intraarticular injections of HA produced a pronounced reduction in pain, significant improvement in physical function and clinical tests of balance. It was a useful and well-tolerated treatment for knee OA, with rapid onset of action at 1 week after the fifth injection and the treatment effects could last for 6 months.

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