# Effect of Intra-articular Injection of Hyaluronic Acid in Rheumatoid Arthritis Patients with Knee Osteoarthritis

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**Background:** Intra-articular injection of hyaluronic acid (HA) is a well-documented treatment for knee osteoarthritis (OA). One of the multifactorial mechanisms is that exogenous HA can stimulate endogenous HA production. HA can regulate the growth and function of chondrocytes by binding to CD44 receptors on the chondrocytes. Synovitis is often found in patients with rheumatoid arthritis (RA) and is supposed to result from CD44 activity. The aim of this study was to investigate the effect of intra-articular injection of HA in patients with RA combined with knee OA.

**Methods:** Twenty RA patients with OA knees were enrolled; 11 patients were placed into a stage II group and 9 into a stage III group, in accordance with the Kellgren-Lawrence classification of knee OA. All patients received intra-articular injection of HA (ARTZ) once a week for 5 weeks, and were evaluated with the WOMAC index (including the pain, stiffness and physical function subscales) at baseline, week 5 and week 9. The Friedman test and Wilcoxon signed rank test with Bonferroni correction method were used for statistical analysis.

**Results:** The effect of intra-articular injection of HA was significant at week 5 ($p < 0.0167$) and persisted to week 9 ($p < 0.0167$). This therapy was equally efficacious with stage II and stage III patients, with no difference between the 2 groups.

**Conclusion:** Intra-articular injection of HA was beneficial in patients with RA combined with knee OA. [*J Chin Med Assoc* 2008;71(8):411–415]

**Key Words:** hyaluronic acid, intra-articular injection, knee osteoarthritis, rheumatoid arthritis

## Introduction

Osteoarthritis (OA) is the most common form of arthritis associated with significant morbidity, and is one of the most common causes of functional limitation and dependency. OA of the knee is characterized by pain, stiffness, decreased joint range of motion and increasing disability. It can have an impact on several aspects of normal life, such as functional and social activities, relationships, socioeconomic status, body image, and emotional wellbeing.[1–4] The earliest lesion of OA is a diminution of mucopolysaccharide and chondroitin sulfate relative to the collagen in the matrix, thereby unmasking the collagen.[1,5–7] For the management of OA, it is important to prevent matrix diminution early and induce matrix synthesis by chondrocytes.

Hyaluronic acid (HA) is a major component of synovial fluid and cartilage. HA plays many key roles in the trophic status of the cartilage and in the regulation of the intra-articular environment. HA is responsible for the viscoelastic properties (shock-absorbing and lubricating abilities) of synovial fluid, which has a lower concentration and molecular weight in OA joints than in healthy ones.[8,9] HA can form a pericellular coat around the cells, interact with proinflammatory mediators, and bind to cell receptors to modulate cell proliferation, migration, and gene expression.[10–14]

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E-mail: cl_chou@vghtpe.gov.tw • Received: February 20, 2008 • Accepted: July 15, 2008



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The molecular weight of HA in the synovial fluid of patients with RA is similar to that of patients with other joint disease, and moderately but significantly lower than that of normal synovial fluid.[15] Serum HA level is raised in patients with early RA and correlates with clinical and laboratory measures of disease activity.[16] The increase in serum HA probably reflects excessive production by the rheumatoid synovium and may serve as an index of inflammation.[17,18] CD44 is a multistructural cell-surface glycoprotein that interacts with many cell-surface and extracellular ligands, the principal one being HA.[19,20] Stimulation of CD44 with HA transmits the signal into the cells, which leads to activation of T cells and cytokine or chemokine release from monocytes. CD44 is overexpressed in inflammatory sites in proportion to the intensity of inflammation.[20,21] CD44 expression is markedly increased in lymphocytes from the synovial fluid of RA patients.[19,22] Arthritis of large joints (in particular, the knee) at first presentation is associated with a destructive course of RA.[23]

Increasing fibrin deposition is a predominant feature of RA in synovial tissue, and contributes to chronic inflammation and progressive tissue abnormalities.[24] Thrombin also acts as a mitogen to stimulate the abnormal proliferation of synovial cells during RA pathogenesis.[25] The inflamed RA synovium is uniquely rich in free HA, which can block the ability of antithrombin to inhibit thrombin, thus driving the pathogenesis of thrombin-related RA.

Intra-articular treatment with HA for OA knee pain is widely accepted. The efficacy and tolerability with OA of the knee have been demonstrated in several clinical trials.[26–29] Inflammation of the knee joint influences the excitability of the nociceptors of the articular nerves. HA can decrease ongoing nerve activity as well as movement-evoked nerve activity.[30] So the therapeutic effect of HA for OA knee pain may be due to the effect of HA on nerve impulses and nerve sensitivity.[3] HA administration can enhance the synthesis of extracellular matrix proteins, including chondroitin, keratin sulfate, and proteoglycans. Exogenous HA can enhance endogenous HA synthesis.[31]

The aim of this study was to investigate the therapeutic effect of intra-articular HA in RA patients with OA knees.

## Methods

### *Patients*

Inclusion criteria were: RA patient with significant OA knee symptoms and signs; radiologically verified knee OA (stage I–III according to the Kellgren-Lawrence classification).[27] Exclusion criteria were: a significantly inflamed OA joint; previous intra-articular injection of steroid or any other invasive procedure in the knee within the previous 6 months; history of intra-articular knee fracture; any other condition that might interfere with the efficiency assessment or trial completion (such as the alternation of drugs for the changing of RA activity).

### *Study design*

All patients received intra-articular injection of HA (ARTZ Dispo; 25 mg/2.5 mL) once a week for 5 weeks. During the study period, all patients did not receive physical therapy for their OA knee problem. We used the WOMAC (Western Ontario and McMaster Universities) index[28] to evaluate the therapeutic effects at baseline (pre-injection), week 5 (after 5 courses of injection) and week 9 (1 month after the last injection). The items on the WOMAC index included 3 dimensions—pain (5 questions), stiffness (2 questions) and physical function subscales (17 questions)—and were rated on an ordinal scale of 0 to 4. Lower scores indicate lower levels of symptoms or physical disability. The validation study reported internal consistencies for the pain, stiffness and physical function subscales of 0.86, 0.86 and 0.95, respectively.[32] Reliability for the pain, stiffness and physical function subscales were 0.68, 0.48 and 0.68, respectively.[33]

### *Statistical analysis*

We used the Friedman test to evaluate the changes in the WOMAC index among the 3 periods of the study. If there was a significant difference ($p<0.05$) among the 3 periods, we used the Wilcoxon signed rank test with Bonferroni correction method to identify which 2 periods were significantly different ($p<0.0167$). In addition, we used the Mann-Whitney U test to compare differences in therapeutic effect.

## Results

Twenty RA patients (1 male, 19 female; mean age, 52.6 years; age range, 32–72 years) with OA knees were enrolled; 11 were placed into a stage II group and 9 were placed into a stage III group. The therapeutic effect of intra-articular HA injection was significant at week 5 ($p<0.0167$) and persisted to week 9 ($p<0.0167$). There was no significant difference between weeks 5 and 9; in each sub-item, the same results were noted (Table 1). For subgroup evaluation, the therapeutic effect in the stage II and stage III groups were

**Table 1.** Results of the Western Ontario and McMaster Universities Osteoarthritis Index*

| | Baseline | Week 5 | Week 9 | *p* |
|---|---|---|---|---|
| | 23.5 (13.0–34.75)<br>Week 5 *vs.* baseline: $p<0.001^{\dagger}$<br>Week 9 *vs.* baseline: $p<0.001^{\dagger}$<br>Week 9 *vs.* week 5: $p=0.121$ | 11.0 (5.5–24.5) | 10.0 (4.0–21.5) | <0.001 |
| Sub-items of WOMAC index in RA ($n=20$) | | | | |
| Pain | 5.0 (3.0–7.0)<br>Week 5 *vs.* baseline: $p<0.001^{\dagger}$<br>Week 9 *vs.* baseline: $p=0.001^{\dagger}$<br>Week 9 *vs.* week 5: $p=0.453$ | 3.0 (1.0–5.75) | 2.5 (0.25–5.75) | <0.001 |
| Stiffness | 2.0 (1.0–3.75)<br>Week 5 *vs.* baseline: $p<0.001^{\dagger}$<br>Week 9 *vs.* baseline: $p=0.001^{\dagger}$<br>Week 9 *vs.* week 5: $p=0.285$ | 1.0 (0.0–2.0) | 1.0 (0.0–1.75) | <0.001 |
| Physical function | 17.0 (8.0–22.75)<br>Week 5 *vs.* baseline: $p<0.001^{\dagger}$<br>Week 9 *vs.* baseline: $p<0.001^{\dagger}$<br>Week 9 *vs.* week 5: $p=0.208$ | 9.0 (4.5–15.5) | 6.0 (3.25–15.75) | <0.001 |

**Data presented as median (interquartile range), Friedman test ($p<0.05$); $^{\dagger}$Wilcoxon signed rank test with Bonferroni correction, $p<0.0167$ is significant.*

**Table 2.** Results of the Western Ontario and McMaster Universities Osteoarthritis Index in rheumatoid arthritis stages*

| | Baseline | Week 5 | Week 9 | *p* |
|---|---|---|---|---|
| Stage II ($n=11$) | 20.0 (11.0–34.0)<br>Week 5 *vs.* baseline: $p=0.003$<br>Week 9 *vs.* baseline: $p=0.005$<br>Week 9 *vs.* week 5: $p=0.66$ | 10.0 (5.0–20.0) | 9.0 (4.0–17.0) | <0.001 |
| Stage III ($n=9$) | 27.0 (17.5–41.5)<br>Week 5 *vs.* baseline: $p=0.007$<br>Week 9 *vs.* baseline: $p=0.028$<br>Week 9 *vs.* week 5: $p=0.722$ | 11.0 (7.5–30.0) | 12.0 (4.5–37.0) | 0.016 |

**Data presented as median (interquartile range), Friedman test ($p<0.05$). There was no significant difference by Wilcoxon signed rank test with Bonferroni correction ($p<0.0167$).*

**Table 3.** Comparison of therapeutic effects between groups*

| | Stage II | Stage III | *p* |
|---|---|---|---|
| Baseline | 20.0 (11.0–31.8) | 27.0 (18.3–40.8) | 0.183 |
| Week 5 | 10.0 (5.5–19.3) | 11.0 (8.8–28.0) | 0.469 |
| Week 9 | 9.0 (4.0–16.5) | 12.0 (5.3–32.0) | 0.361 |

**Data presented as median (interquartile range), Mann-Whitney U test.*

grossly of the same effectiveness but not significantly different ($p<0.05$ but not $<0.0167$; Table 2) according to the WOMAC index evaluation. There were no significant differences between the groups with regard to therapeutic effect (Table 3), and there were no adverse effects during treatment.

## Discussion

OA is not a simple wear-and-tear phenomenon, but is an active process that is part of the reparative response to injury.[1] Ghosh and Guidolin[34] found that HAs with a molecular weight within the range of $0.5\times10^6$ to $1.0\times10^6$ Da (such as the ARTZ used in this study) are generally more effective in reducing indices of synovial inflammation and restoring the rheologic properties of synovial fluid than HAs with a molecular weight of more than $2.3\times10^6$ Da. Evidence of partial restoration of normal joint tissue metabolism was noted in an animal model study.[35] Intra-articular HA used for the treatment of OA knee pain is a multifactorial mechanism. HA can reduce the symptoms of OA by mitigating

the activities of proinflammatory mediators and pain-producing neuropeptides released by activated synovial cells.[1,3,34–36] The partially restored synovial fluid's rheologic properties and synovial fibroblast metabolism in animal models were compatible with joint pain reduction and improvement of functional status.[36] Furthermore, the use of intra-articular HA injection can delay the need for surgery in patients who are candidates for total knee replacement.[37]

The most common adverse events that occur with HA injection are local knee pain and/or swelling, which were seen in 2.2% of injections, or in 7.2% of patients,[38] but there were no local adverse events in our study.

The proinflammatory cytokines interleukin-1 and tumor necrosis factor-α stimulate the expression of HA synthetase,[39] which may contribute to the fragmentation of HA under inflammatory conditions. Fragmented HA (< 500 kDa), rather than high-molecular-weight HA (> 1 MDa),[40] stimulates cell-surface CD44 receptors, leading to intracellular signaling, gene activation and the expression of proinflammatory mediators. Low-molecular-weight fragments of HA also stimulate angiogenesis,[41] an important factor in inflammation. CD44 adhesion to HA has been shown to mediate chondrocyte proliferation and function.[42] Exogenous HA may facilitate the production of newly synthesized HA.[3,31]

The rationale for intra-articular HA therapy (as in our study) has been to replace degraded HA with high-molecular-weight polysaccharide. The therapeutic effect of injected high-molecular-weight HA may be due to an increase in the local concentration, rather than a major change in the molecular weight properties of the synovial polysaccharide. Systemic or local steroid treatment, which is usually used for the management of RA, had no effect on the concentration or molecular weight of HA.[15] Corticosteroid seems to be rather active in reducing the inflammatory process, whereas HA seems to influence mostly the number and distribution of lining cells and to stimulate the reparative processes of OA.[43] There is no evidence-based therapeutic effect for combined therapy with steroid and HA.

Pitsillides et al[44] found that the ratio of free HA to bound HA was significantly increased in RA. The high concentration of free HA in diseased RA synovium locally blocks antithrombin under physiologic conditions and thereby deregulates the activity of thrombin.[25] Some clinical studies have shown that injecting HA into articular rheumatoid joints can ameliorate inflammation.[45,46] Determining the exact mechanism by which HA inhibits antithrombin requires further investigation.

Our study showed that intra-articular HA injection was beneficial in RA patients with OA knees. The therapeutic effect is significant as evidence-based in other OA knee patients (not under the influence of stable RA itself). Though subgroup analysis (stage II and stage III) showed no statistically significant difference, it may be due to the small sample size in each group. This is the major limitation of our study.

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