# Use of Hyaluronan Sodium (Adant) in Knee Arthrosis

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## ABSTRACT

**Objective:** To find out the clinical effects and safety of intra articular injection of hyaluronan sodium (Adant), the study was carried out as an open trial with 12 month follow up.

**Materials and Method:** From 2003 to 2006, 46 patients who had moderate osteoarthritis of their knees, Ahlback radiographic classification grade III and IV, were enrolled in our trial. Their average age was 67.61 + 9.05 years ranging from 47 to 80 years; average height was 155.33 + 7.47 cm; and average weight was 66.53 + 9.92 Kg. The average BMI of the patients was 27.70 + 4.14. All patients had received intensive conservative treatment of osteoarthritis of the knee but all still continuously needed non-steroidal anti-inflammatory drugs for more than 3 months because of pain. All patients received two milliliters of hyaluronan sodium (Adant) intra articularly once a week for five weeks and they were followed up monthly after the last injection for 12 months. Goldberg knee function score and visual analog scale were used to measure the clinical effects of the drug. Knee function score and visual analog scale were reevaluated in every follow up. The amount of NSAIDs used was also recorded and used as an indirect indicator of improvement. Global evaluations about the benefit of the treatment by the doctor in charge and the patients themselves were also carried out.

**Results:** Thirty six patients were classified as Ahlback III and 10 patients as Ahlback IV. Thirty one patients were able to complete the trial. At 12 month follow up, 14 patients had significant improvement and NSAIDs could be discontinued. Eleven patients had an improvement; however, occasional NSAIDs administration for a short period of less than 2 weeks was still needed. Five patients still needed NSAIDs as they did before the trial and the rest (one patient) became worse and surgical treatment was advised. No significant side effect was observed.

**Conclusion:** Intra articular administration of hyaluronan sodium (Adant) gave encouraging results in the treatment of osteoarthritis of the knee with moderate changes at one year follow up.

## INTRODUCTION

Osteoarthritis is the most common type of articular diseases in orthopaedic practice. This is an idiopathic joint disease characterized by an imbalance between synthesis and degradation of articular cartilage and subchondral bone accompanied by capsular fibrosis, osteophyte formation and variable grade of inflammation of synovial membrane. Joint lubrication is naturally provided by hyaluronic acid in synovial fluid. Hyaluronic acid is presented in abundance in normal young and healthy joints. In osteoarthritis hyaluronic acid is smaller in size, molecular weight and diminished in concentration. This condition can increase wear and tear process of the joint that results in pain and inflammation. The decrease in joint lubrication and degradation of shock absorbing mechanism in osteoarthritis can be remedied by intra-articular viscosupplementation[1-3]. Increasing synovial fluid viscosity can improve boundary lubrication of the affected joint and allows natural healing process to take over. This findings brings the concept of viscosupplementation into clinical practice by the use of hyaluronan intra articular injection[4-8]. Hyaluronan sodium, Adant, is a form of hyaluronic acid with a molecular weight of about 1.0 million Dalton. It has been used as viscosupplementation by intra articular application in osteoarthritis of the knee with encouraging results[5]. This study was carried out to study more details about its clinical effects and safety,

## MATERIALS AND METHOD

This trail was carried out during 2003 to 2006 at the Department of Orthopaedic Surgery, Faculty of Medicine, Siriraj Hospital, the Department of Orthopaedic Surgery, Faculty of Medicine, Thammasat University and the Department of Orthopaedic Surgery,

Promongkutkao Hospital. This trial was approved by the ethic committee of the Faculty of Medicine, Siriraj Hospital. It was designed as an open trial of 46 patients who had primary knee osteoarthritis and could be treated as ambulatory patients. The drug (Adant) was supplied by Thai Meji company. The company also covered all expenses of the patients during the trial. Inclusion criteria were 1) patients who had clinical signs and symptoms of primary osteoarthritis of their knees and were clinically and radiologically ascertained as such for more than 1 year according to the American College of Rheumatology criteria[9], 2) patients who had moderate knee osteoarthritis with radiographic grading Ahlback III and IV[10] and 3) patients who needed any kind of NSAIDs continuously for more than 3 months or had signs and symptoms of the side-effects of NSAIDs. Exclusion criteria were 1) patients who received intra-articular steroid injection within 6 months or intra-articular injection of chondro-protective agents within 1 year, 2) patients who had severe knee deformities, varus or valgus more than 15 degrees on true antero-posterior radiograph of the weight-bearing knee, 3) patients who had an unstable knee from previous internal derangement, 4) patients who had marked arthritis in both knees, 5) patients who had skin diseases around their knees, 6) patients who had uncontrolled diabetes mellitus and other endocrine diseases, 7) patients who had osteoarthritis of the knee with severe degenerative diseases of their spines and 8) uncooperative patients.

Before the trial, a complete investigation including complete blood count, urine analysis, blood tests for renal and liver function, including uric acid and plain radiograph of their knees was carried out to confirm the diagnosis and to rule out any uncontrolled underlying diseases. All patients needed to have normal results from the investigation. The patients were evaluated of their maximum pain severity by visual analog scale (VAS, 0 to 100 mm) during the follow up period. Goldberg knee score was used to evaluate patients' knee functions [11] (Tab 1).

Subsequently, intra-articular injection of hyaluronan sodium once a week for five weeks was performed under sterile technique in all patients, by only three orthopaedic surgeons. The drug was administered via supero-lateral approach above the patellar with the patients in supine position. Patients' pain severity was evaluated by using visual analog scale. For patients' knee functions, Goldberg knee scoring was used. The patients were followed up every month after the last injection for 12 months. The patients were allowed to use NSAIDs and acetaminophen as needed and the dosage of these drugs was readjusted according to pain and disability. Changes of the need of NSAIDs and acetaminophen were also evaluated and used as indirect indicators to evaluate the clinical efficacy of intra-articular hyaluronan administration. Overall evaluations by the patients were also recorded. A very good result was noted when the patients had only mild pain, NSAIDs could be discontinued and only acetaminophen was needed occasionally. Good result was noted when the patients had infrequent pain that needed NSAIDs for only a short period of time, for less than 2 weeks during the follow-up period. No change was noted when the patients still needed NSAIDs regularly as they did before the trial and a worse result was noted when the patients had more pain and poorer knee functions. Any abnormal signs and symptoms of every system were monitored and recorded descriptively.

## RESULTS

There were 46 patients in our study. Six patients were male and 40 patients were female. Their average age was 67.61 + 9.05 years ranging from 47 to 80 years; Average height was 155.33 + 7.47 cm; and average weight was 66.53 + 9.92 Kg. The average BMI of the patients was 27.70 + 4.14. The joint treated with the drug was left knee in 28 patients and right knee in 18 patients. Thirty six patients had a radiographic grading as Ahlback III and 10 patients were graded as Ahlback IV (Table 2). Concerning knee pain, average VAS of the patients was 64.13 + 19.69. Average Goldberg functional knee score of the patients was 56.39 + 14.27. Before the trial drug administration, the average VAS of the maximum pain on daily living during the preparation period was 64.1 + 19.7. Goldberg functional knee score before the trial ranged from 56.39 + 14.27. Ten patients had mild degree of degenerative diseases of their spines. Two patients had diabetes mellitus and three patients had hypertension that was under controll.

At 1-month follow up, there were 46 patients underwent reevaluation. Thirty patients' self-evaluations revealed that they had much improvement and NSAIDs could be discontinued. These patients were in the very good responder group. Eleven patients had improvement, but occasional use of NSAIDs for less than three weeks was still needed. They were in the good responder group. Four patients

evaluated that there was no change and one patient became worse. Regarding pain, the average VAS of maximum pain during the last one month was significantly reduced from 64.13 + 19.69 at the period before trial down to 26.7 + 25.3, $p < 0.001$. The mean knee function score was also significantly improved from 56.39 + 14.27 at before trial to 79.67 + 10.79, $p < 0.001$.

There were 45 patients who underwent the 3-month follow up. Twenty eight patients' self-evaluation revealed that they had very good results, while 10 patients had good results. However, seven reported that they had no change in pain severity. Regarding pain, the average VAS of the maximum pain during the last 3 months was 30.22 + 25.2. The mean knee function score was 78.69 + 13.24.

At 6-month follow up, there were 41 patients to be followed up. Twenty four patients' self-evaluation revealed that they had very good results while 11 patients had good results, 5 reported no change and one became worse. Regarding pain, the average VAS of the maximum pain during the last 3 months was 31.7 + 27.5. The mean knee function score was 74.9 + 17.9.

At 12-month follow up, there were 31 patients who attended the follow up evaluation. Seventeen patients' self-evaluation revealed that they had very good results, while 9 patients had good results, 4 patients were in the no change group and 1 patient became worse and surgical treatment was planned for her. Regarding pain, the average VAS of the maximum pain during the last six months was 24.7 + 22.8 and it was still less than before trial. The mean knee function score was 75.6 + 17.1 and that was still higher than before the trial.

## DISCUSSION

Various kinds of treatment are used to control pain and improve knee function. Combinations of pharmacological and non-pharmacological treatments are usually needed. Surgical treatment is still the final choice of treatment and various types of conservative treatment should first be applied to most of the patients.

Viscosity of the synovial fluid can be compromised by the process of inflammation. In osteoarthritis, the degenerative process in the synovial membrane produces poor quality of synovial fluid production[1,2,3,12]. Synovial fluid in osteoarthritis has low viscosity, low mucin content and a very low molecular weight hyaluronic acid. This kind of synovial fluid has poor boundary lubrication property and poor modulation of weight bearing during motion[1,2,3].

The trial hyaluronan sodium (Adant) contains medium molecular weight hyaluronic acid, about 1.0 million Dalton. Biological activities of intra articular injection of hyaluronic acid are 1) inhibition of prostaglandin E2 synthesis induced by IL-1 at synoviocytes, 2) influences on leukocyte adherence, proliferation and migration and 3) protection against proteoglycan depletion and cytotoxicity induced by free radicals[13]. Intra articular injection of hyaluronic acid can improve the viscosity and boundary lubrication of osteoarthritic joint which may slow down the process of degeneration and improve joint function[14-17]. This treatment is named viscosupplementation which is proved to be an effective treatment for patients with knee arthrosis who have an ongoing pain or are unable to tolerate a conventional conservative treatment. Furthermore, hyaluronic acid may prevent degeneration of chondrocytes as the addition of hyaluronic acid into a chondrocyte culture with disaggregated proteoglycan induces better proteoglycan production[18]. Better quality of synovial fluid production was also observed after an introduction of hyaluronic acid into a synovial cell culture[2].Intra articular hyaluronic acid administration is also recommended as a tool for the treatment of osteoarthritis, particularly in patients for whom surgical treatment is not justified or is not suitable due to underlying diseases[8]. As viscosupplementation administration has a very low risk, it can be used safely[19]. Temporary aseptic synovitis and pseudo gouty arthritis was found in some reports after administration of hyaluronan with ultra high molecular weight [20]. Some authors reported no difference between intra articular hyaluronic acid injection and intra articular steroid injection after short term follow up[21,22]. However, pain and inflammation in the patients who received hyaluronan were decrease after 6 month-follow up. Viscosupplementation appears to have a slower onset of action than intra-articular steroids, but the effect seems to last longer[22].

Concerning the choice of molecular weight of intra articular hyaluronic acid, some authors preferred a rather low molecular weight. They proposed that small molecule hyaluronic acid has a better effect on

inflammatory receptors[17,21,23]. However, others preferred to use large or ultra large molecule hyaluronic acid as it can improve the viscosity of the synovial fluid better and it also has better physical property of weight protection for the articular cartilage[17,21,23]. In this study, a medium molecular weight hyaluronan was used.

Significant reduction in pain and improvement of knee function after hyaluronan administration were observed beginning at 1-month follow up. This finding revealed rapid onset of pain reduction and improvement of knee function of the trial hyaluronan. Furthermore, about 80% of the patients were in the very good and good responder group, Table 4 and 5. NSAIDs could be discontinued in these patients.

The trial hyaluronan had long lasting effect about 9 - 12 months. Most of the patients, 26/46 or 56.5 %, still had very good to good results at 12 month follow up. Fifteen patients could not complete the follow up evaluation and were classified as poor response patients. Pain also lessened in these patients and average pain severity at 12 month follow up was still significantly lower than before the trial. From Goldberg scoring, the patients still had significant improvement of their knee function at 12 month follow up and the average score was still higher than before trial. More than fifty percents of the patients could stop using NSAIDs after the injection. Complications from the use of NSAIDs were minimal.

## CONCLUSION

Intra articular hyaluronan with medium molecular weight (Adant) gave persuasive results in the treatment of osteoarthritis of the knee in patients who had a mild to moderate degree of osteoarthritis which was evaluated by radiographic study; the good to very good effects could last from 6 to 12 months.

**Table 1.** Goldberg functional knee score [11]

| | |
|---|---|
| 1. Pain | |
| a. None/ignores | 44 |
| b. Slight,occasional, no compromise in activity | 40 |
| c. Mild, no effect on ordinary activity, pain after unusual activity | 30 |
| d. Moderate, tolerable, makesconcessions | 20 |
| e. Marked, serious limitations | 10 |
| f. Totally disabled | 0 |
| 2. Function | |
| a.Gait (Walking maximum distance) | |
| 1.Limp : | |
| None | 3 |
| Slight | 2 |
| Moderate | 1 |
| Serious | 0 |
| Unable to walk | 0 |
| 2. Support : | |
| None | 11 |
| Cane, long walks | 7 |
| Cane, full time | 5 |
| Crutch | 4 |
| 2 canes | 2 |
| 2 crutches or walker | 0 |
| Unable to walk | 0 |
| 3. Distance walked : | |
| Unlimited | 11 |
| 6 blocks | 8 |
| 2-3 blocks | 5 |
| Indoors only | 2 |
| Bed and chair | 0 |
| b. Functional activities | |
| 1. Ability to use stairs : | |
| Ascends and descends normally | 6 |
| Ascends normally, has diffi-culty descending | 4 |
| Uses banister at all times | 2 |
| Unable | 0 |
| 2. Ability to get out of chair : | |
| Able with ease | 5 |
| Able with difficulty | 3 |
| Unable | 0 |
| 3. Ability to sit in car or theater : | |
| No difficulty | 1 |
| Difficulty | 0 |
| 3. Absence of deformity | |
| a. None | 2 |
| b. Varus or valgus, 10° | 0 |
| c. Flexion contracture, 10° | 0 |
| 4.Range of motion | |
| Add each segment to arc to determine total score. | |
| Do not add point if any portion of arc is missing. | |
| Flexion | |
| 0° - 15° | 2 |
| 15° - 45° | 2 |
| 45° - 90° | 2 |
| 90° or greater | 1 |
| 5. Stability | |
| a. Never locks or gives way | 7 |
| b. Rarely locks or gives way | 5 |
| c. Frequently locks or gives way | 0 |
| 6. Effusion or haemarthrosis | |
| a. Never has an effusion | 3 |
| b. Occasionally has an effusion | 1 |
| c. Frequently has an effusion | 0 |
| 7. Total knee function rating..... | |
| Compensation or litigation involved? | Yes/No |

**Table 2.** Biographic data and pathology of the patients

| Biographic data | Male(n=6) | Female(n=40) | Total (n=46) |
|---|---|---|---|
| Age (years) | 75.50 ± 6.66 | 66.43 ± 8.82 | 67.619.05 |
| Body weight (Kg) | 66.25 ± 4.79 | 66.5710.45 | 66.539.92 |
| Height (cm) | 158.75 ± 8.10 | 154.897.41 | 155.337.47 |
| BMI | 26.321.52 | 27.874.35 | 27.704.14 |
| Ahlback grading | | | |
| III Minor bone attrition< 0.5 cm. | 5 (11%) | 31 (68%) | 36 (78%) |
| IV Moderate bone attrition 0.5 -1.0 cm. | 1 (2%) | 9 (19%) | 10 (22%) |
| Sides of drug injection | | | |
| Left | 3 (50.0%) | 25 (62.5%) | 28 (60.9%) |
| Right | 3 (50.0%) | 15 (37.5%) | 18 (39.1%) |

**Table 3.** Changes of pain severity, VAS, and Goldberg functional score before and after drug administration

| | Before trial (n = 46) | 1st month (n = 41) | 3rd month (n = 44) | 6th month (n = 41) | 12th month (n = 31) |
|---|---|---|---|---|---|
| VAS | 64.13+19.69 | 29.96+23.55 | 30.22+25.24 | 31.70+27.55 | 24.67+22.76 |
| Paired t-test with Bonferroni correction | | < 0.001 | | | |
| Goldberg score | 56.39+14.27 | 77.32+14.16 | 78.37+13.64 | 74.87+17.98 | 75.61+17.09 |
| Paired t-test with Bonferroni correction | | < 0.001 | | | |

**Table 4.** Global evaluation by the patients

| | At the 5th injection (n = 46) | 3rd month (n = 44) | 6th month (n = 41) | 12th month (n = 31) |
|---|---|---|---|---|
| Very good | 30 (65.2%) | 28 (63.6%) | 24 (58.5%) | 17 (54.8%) |
| Good | 11 (23.9%) | 10 (22.7%) | 11 (26.8%) | 9 (29.0%) |
| No improvement 4 (8.7%) | 6 (13.7%) | 5 (12.3% ) | 4 (13.0%) | |
| Worse | 1 (2.2%) | 0 (0%) | 1 (2.4%) 1 (3.2%) | |

**Table 5.** Global evaluation by the orthopaedic surgeons in charge

| | At the 5th injection (n = 46) | 3rd month (n = 44) | 6th month (n = 41) | 12th month (n = 31) |
|---|---|---|---|---|
| Very good | 15 (32.6%) | 24 (53.3%) | 23 (56.1%) | 14 (45.2%) |
| Good | 23 (50.0%) | 13 (28.9%) | 9 (24.4%) | 11 (35.4%) |
| No improvement 7 (15.2% | 7 (17.8%) | 8 (17.1%) | 5 (16.2%) | |
| Worse | 1 (2.2%) | 0 (0%) | 1 (2.4%) 1 (3.2%) | |

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