

Intra-Articular Hyaluronic Acid as Treatment in Elderly and Middle-Aged Patients with Knee Osteoarthritis

Demet Uçar^{*1}, Demirhan Dıraçoğlu², Türker Süleyman² and Nalan Çapan²

¹Department of Physical Medicine and Rehabilitation, Dicle University Medical Faculty, Diyarbakir, Turkey

²Department of Physical Medicine and Rehabilitation, Istanbul University Medical Faculty, İstanbul, Turkey

Abstract: *Introduction:* Osteoarthritis is the most common age-related degenerative joint disease. It affects all the joints containing hyaline cartilage. Knee osteoarthritis is the most cumbersome in terms of prevalence and disability. The aim of this study to evaluate the efficacy of intra-articular hyaluronic acid in patients with knee osteoarthritis with regard to joint pain and function, as well as patient satisfaction, assessed at one month and at one year, and by age group.

Methods: In this prospective randomised study, 172 patients who were diagnosed knee OA and who received three consecutive intra-articular injections of HA weekly were included. Patients 65 years of age or older were accepted as the “elderly group”, and those under 65 were accepted as the “middle-aged group”. Clinical evaluations of efficacy and safety were conducted at the beginning of the study, one month after the third injection, and one year after the third injection.

Results: In the two groups, the intragroup analysis revealed significant improvements following injection when compared with preinjection values. According to the last followup controls (after 12 months) in the middle-aged group, VAS activity pain, VAS rest pain, WOMAC physical function, and WOMAC pain values were found to be statistically lower when compared with pre-injection values. In the elderly group, no statistically significant differences were found between pre-injection and after 12 months.

Conclusion: We can conclude that intra-articular joint HA injections are effective in both young and old patients with OA with regard to pain and functional status over a short-term period. Further, HA injections in patients younger than 65 years can be planned for a one-year period.

Keywords: Knee osteoarthritis, hyaluronic acid, knee pain.

INTRODUCTION

Osteoarthritis (OA) is the most common age-related degenerative joint disease and one of the most important health problems in the world. It affects all the joints containing hyaline cartilage. Although OA can affect any synovial joint, OA of the knee joints is the most cumbersome in terms of prevalence and disability [1]. Primary symptoms of the disease are pain and tenderness in the joint [2]. Hyaluronic acid (HA), a mucopolysaccharide comprised of tandem repeats of D-glucuronic acid and N-acetyl glucosamine, is abundantly present in synovial fluid [3]. Intra-articular administration of HA is the treatment of choice for patients with symptomatic knee OA [4]. The effects of HA have been reported up to one year in most studies; however, age-related outcomes in knee OA have not been emphasized as much as they should [4-7]. Because the effect of age on treatment effectiveness has not been assessed much in previous studies, it might be interesting to gather data on this particular issue. Thus, we aimed to evaluate the efficacy of intra-articular HA in patients with knee OA with regard to joint pain and function, as well as

patient satisfaction, assessed at one month and at one year, and by age group (65 and over and under 65).

PATIENTS AND METHODS

In this prospective randomised study, 172 patients who were diagnosed knee OA according to the American College of Rheumatology (ACR) criteria [8] and were classified with radiological stage II or III according to the Kellgren and Lawrence classification [9] were recruited from the medical files in our outpatient injection clinic.

Patients who received three consecutive intra-articular injections of HA (30mg/2 ml) weekly were included in the study. The knee joint injections were performed under sterile conditions by inserting a 21-gauge needle into the patellofemoral joint space by superolateral approach while the patients were in a supine position. Patients 65 years of age or older were accepted as the “elderly group” (n=71), and those under 65 were accepted as the “middle-aged group” (n=101). In both groups, pain level during activity and at rest was measured using a visual analog scale (VAS). Western Ontario and McMaster University Osteoarthritis Index (WOMAC 5-point Likert 3.0) [10] and VAS were used to analyze pain, stiffness, disability, and functional status. Clinical evaluations of efficacy and safety were conducted at the beginning of the study, one month after the third injection, and one year after the third injection. At

*Address correspondence to this author at the Dicle University Medical Faculty, Diyarbakir, Turkey; Tel: 0090 4122488001; Fax: 0090 4122488111; E-mail: drdemetucar@yahoo.com

month 12, a followup telephone interview was conducted by the evaluator to assess long-term efficacy and safety. The patients were questioned during the followup telephone interview regarding adverse signs and symptoms that had emerged during the study period. Exclusion criteria were previous intra-articular injections, history of knee trauma or knee surgery, inflammatory knee disorders, metabolic bone disease, serious systemic disease, depression, neoplasm, and effusion in the knee.

Outcome measures were analyzed using the SPSS package; data was shown as mean plus/minus standard deviation. We used a chi-square test to compare the radiological grades of the cases of the two groups. An independent samples t-test was used to compare the WOMAC and VAS scores of the two groups. Intra-group comparisons before and after the injections were measured by using a paired sample t test. A p-value less than 0.05 was accepted as statistically significant.

RESULTS

The mean age was 71.3 years (65–84) in the elderly group and 54.5 years (34–64) in the middle-aged group. According to the Kellgren and Lawrence classification, the cases of the two groups and gender of the patients were found correlated (Table 1). Pre-injection values of the patients are summarized in Table 2. The two groups were statistically similar in this regard.

Table 1. Radiological Grades and Genders of the Patients

| | Grade II (n) | Grade III (n) | Female (n) | Male (n) | Total (n) |
|------------------|--------------|---------------|------------|----------|-----------|
| Middle-age group | 36 | 65 | 74 | 27 | 101 |
| Elderly group | 24 | 47 | 56 | 15 | 71 |
| P value | 0.803 | | 0.399 | | |

Table 2. Pre-Injection Values in the Two Groups

| | Middle-Age Group | Elderly Group | P Value |
|-------------------------|------------------|---------------|---------|
| VAS resting pain | 4.4 ± 2.9 | 4.4 ± 2.8 | 0.963 |
| VAS activity pain | 7.3 ± 1.8 | 7.6 ± 1.8 | 0.317 |
| WOMAC pain | 4.9 ± 1.7 | 5.1 ± 1.8 | 0.608 |
| WOMAC stiffness | 4 ± 2.6 | 4.4 ± 2.3 | 0.309 |
| WOMAC physical function | 4.9 ± 1.9 | 5.3 ± 1.8 | 0.167 |
| WOMAC total | 13.7 ± 5.2 | 14.7 ± 4.8 | 0.206 |

In the two groups, the intragroup analysis revealed significant improvements in VAS activity pain, VAS rest pain, WOMAC pain, WOMAC stiffness, WOMAC physical function, and WOMAC total values following injection when compared with preinjection values (Tables 3 and 4). Although not statistically significant (p>0.05), the comparison of the differences (pre-injection/post-injection) between the groups revealed higher values in the middle-aged group.

Table 3. Post-Injection Values in the Middle-Age Group

| | Postinjection | P Value * |
|-------------------------|---------------|-----------|
| VAS resting pain | 2.6 ± 2.4 | < 0.001 |
| VAS activity pain | 5.3 ± 2.5 | < 0.001 |
| WOMAC pain | 3.7 ± 1.9 | < 0.001 |
| WOMAC stiffness | 2.6 ± 1.7 | < 0.001 |
| WOMAC physical function | 3.9 ± 1.9 | < 0.001 |
| WOMAC total | 10.4 ± 5.3 | < 0.001 |

*: Comparison with the pre-injection values.

Table 4. Post-Injection Values in the Elderly Group

| | Postinjection | P Value * |
|-------------------------|---------------|-----------|
| VAS resting pain | 2.4 ± 2.3 | < 0.001 |
| VAS activity pain | 4.6 ± 2.2 | < 0.001 |
| WOMAC pain | 3.5 ± 1.4 | < 0.001 |
| WOMAC stiffness | 3.1 ± 1.9 | < 0.001 |
| WOMAC physical function | 3.6 ± 1.5 | < 0.001 |
| WOMAC total | 10.1 ± 4 | < 0.001 |

*: Comparison with the pre-injection values.

According to the last followup controls (after 12 months) in the middle-aged group, VAS activity pain, VAS rest pain, WOMAC physical function, and WOMAC pain values were found to be statistically lower when compared with pre-injection values, while no significant differences were detected in WOMAC stiffness and WOMAC total values (Table 5). In the elderly group, no statistically significant differences were found between pre-injection and after 12 months (Table 6).

Table 5. Values After 12 Months in the Middle-Age Group

| | After 12 Months | P Value * |
|-------------------------|-----------------|-----------|
| VAS resting pain | 3.7 ± 2.5 | < 0.001 |
| VAS activity pain | 7 ± 1.9 | 0.001 |
| WOMAC pain | 4.8 ± 1.8 | 0.009 |
| WOMAC stiffness | 3.9 ± 2.1 | 0.466 |
| WOMAC physical function | 4.8 ± 1.9 | 0.004 |
| WOMAC total | 13.5 ± 4.8 | 0.11 |

*: Comparison with the pre-injection values.

No adverse events occurred in any of the patients due to the injections.

DISCUSSION

In 1934, Meyer and Palmer isolated a polysaccharide from bovine vitreous humor and named it hyaluronic acid [3]. The first therapeutic studies of viscosupplementation with HA in knee OA in humans were reported by Rydell and

Balazs [11]. In recent years, viscosupplementation with HA products has been used frequently in the management strategy of primary knee OA [12-16].

Table 6. Values After 12 Months in the Elderly Group

| | After 12 Months | P Value * |
|-------------------------|-----------------|-----------|
| VAS resting pain | 4.3 ± 2.7 | 0.103 |
| VAS activity pain | 7.5 ± 1.8 | 0.32 |
| WOMAC pain | 5 ± 1.7 | 0.083 |
| WOMAC stiffness | 4.2 ± 2.1 | 0.07 |
| WOMAC physical function | 5.2 ± 1.6 | 0.321 |
| WOMAC total | 14.4 ± 5.2 | 0.161 |

*: Comparison with the pre-injection values.

A meta-analysis by Aggrawal [17] reported that administration of viscosupplementation with HA to the knee joint is a good therapeutic choice in patients who do not respond to conservative treatment or who are not eligible for surgery. In their recent meta-analysis of randomized controlled trials, Wang *et al.* [13] confirmed that intra-articular injection of HA can decrease symptoms of knee OA. We observed good outcomes in our study as well.

The impact of age and radiological degree of osteoarthritis on clinical efficacy is unclear. To date, the ideal candidate for intra-articular visco supplementation has yet to be clearly defined, with the majority of clinical studies treating patients over 60 years of age with moderate to severe OA. Despite clinical evaluations, age, symptoms, and disease severity have not proven helpful in identifying the patients who might benefit the most. Some studies suggest that patients older than 65 years and with those with advanced radiographic stage arthritis were less likely to benefit from intra-articular injection of HA [13,18]. However, other studies have suggested the opposite, in favor of an older population with more severe knee disease, as these patients may be more sensitive in detecting an analgesic effect [19, 20]. In this study, we are unable to provide any additional information about severe disease (Grade IV), as all the cases were grade II or III. We found a better outcome in the middle-aged group. In particular, the results after 12 months were better in patients younger than 65 years.

In one meta-analysis, it was demonstrated that significant improvements, with limited undesirable effects, were found in terms of activity pain, resting pain, and functional status [13]. However, Arccih *et al.* [21] indicated that most of the relevant trials had low methodological quality and that, although HA was superior to placebos with respect to the effects on activity pain, it was not effective on resting pain and did not enhance joint function. Significant improvements in pain, functional status, and duration of pain-free walking have been observed in such studies [21-24]. Our post-injection results demonstrated that intra-articular HA injection in either of these two groups might provide significant improvements in VAS activity, VAS rest, and WOMAC total. Moreover, after 12 months, beneficial effects were seen in the middle-aged group in terms of VAS

activity, VAS rest, WOMAC pain, and WOMAC physical function. The most important limitation of our trial was the lack of long-term followup; as such, our results are applicable for patients with grade II or III.

CONCLUSION

To summarize, in light of our results, we can conclude that intra-articular joint HA injections are effective in both young and old patients with OA with regard to pain and functional status over a short-term period. Further, HA injections in patients younger than 65 years can be planned for a one-year period. Long-term followup results after such injections remain to be investigated in future studies.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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