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PŮVODNÍ PRÁCE

Safety and Efficacy of Intra-Articular 20 mg/2 ml Hyaluronic Acid Injection for the Non-Operative Palliation Treatment of Osteoarthritis of the Knee Joint

Bezpečnost a účinnost intraartikulární injekce 20 mg/2 ml hyaluronové kyseliny v konzervativní paliativní léčbě osteoartrózy kolenního kloubu

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ABSTRACT

PURPOSE OF THE STUDY

In this study it is aimed to prospectively evaluate the safety and efficacy of 20 mg/2 ml Hyaluronic Acid (HA) injections for non-operative palliation treatment of osteoarthritis (OA) of the knee joint.

MATERIAL AND METHODS

After institutional review board approval was obtained for the study, 63 patients were enrolled and followed prospectively. All the patients have signed informed consent form.

Patients who had diagnosis of gonarthrosis according to clinical and radiological evaluation, were given nonsteroid anti-inflammatory drug (NSAID) treatment for four weeks. Patients between 55–80 years old in both sexes, whose pain did not relieve were included to the study and were followed up for 6 months. They were applied HA injections in total; three times with one week of interval. Patients were evaluated three times during the study. First one at third week (at the control visit of third injection), secondly at third month and lastly at sixth month.

Western Ontario and McMaster Universities Osteoarthritis (WOMAC) and Short Form Health Survey (SF-36) scores were used to clinically evaluate the patients at follow ups.

RESULTS

56 (88.9%) patients completed the study and 7 (11.1%) patients did not show up for follow-up examinations and they were excluded. The mean age of the patients was 63.6 ± 6.90 (range 47 and 76) years old. 22 (39.2%) of the patients were male and 34 (60.7%) were female. Any adverse events and adverse effects were not seen in the enrolled patients group.

CONCLUSIONS

Results of this study revealed that the use of 20 mg/2 ml HA injection was effective in improving the WOMAC index score in patients of knee OA. Additionally, patients' quality of life as measured by SF-36 questionnaire was also significantly improved at the end of the study. None of the patient reported any of the adverse events during the study. Overall, the 20 mg/2 ml HA injection can be considered as a good treatment option for the knee OA in patients who do not respond to non-pharmacological therapy, NSAIDs or analgesics.

Key words: osteoarthritis, hyaluronic acid, injection, non-operative.

INTRODUCTION

Osteoarthritis (OA) is the leading cause of lower-limb disability in older adults world-wide, contributing to pain, stiffness and functional limitation as well as having a negative impact on the physical and mental well-being of patients (17). The pathogenesis of knee OA is multifactorial, but largely attributable to chronic overloading of the knee joint that promotes degradation of the articular cartilage (1). Hyaluronic acid (HA) is an integral component of synovial fluid. As part of its intra-articular function, it acts as a joint lubricant during shear stress and a shock absorber during compressive stress. Loss of hyaluronic acid appears to contribute to joint pain and stiffness. Among adults 60 years of age or older the prevalence of symptomatic knee OA is approximately 10% in men and 13% in women (6, 19, 24). The etiology of knee OA is not entirely clear, but its incidence increases with age, particularly in women (1, 19, 20). Obesity is considered as one of the main risk factor for the development and progression of OA along with other genetic or traumatic factors (11).

Analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are considered to be the first line treatment options (6, 7, 10, 15, 18, 19). However, due to the known facts of NSAIDs causing potential systemic side effects, caution must be taken before prescribing NSAIDs to the elderly patients who consists the main population of OA (19). Recent publications recommend conservative therapy as the first-line OA management, focusing on weight loss, strength training, water and land-based exercise followed by pharmacologic measures including NSAIDs and intra articular injection of HA (10, 18, 19). Both long- and short-term therapeutic effects of HA in knee

OA patients have been shown in various clinical trials in comparison to intra-articular injection of corticosteroids and placebo (7, 19). However HA applications and dosage are still controversial. In OA, viscoelastic properties of synovial fluid decrease due to the degradation of endogenous HA (18). Intra-articular injection of exogenous HA stimulates production of endogenous HA which may relieve symptoms of knee OA via multiple pathways (10). Besides structural benefits, HA has short term performance due to analgesic effect and also has long term effect which helps in pain and joint function (2). The best therapeutic results of using low molecular weight HA were observed with a dose range between three to five weekly intra-articular injections, each with 2 to 2. 5 ml of HA (14).

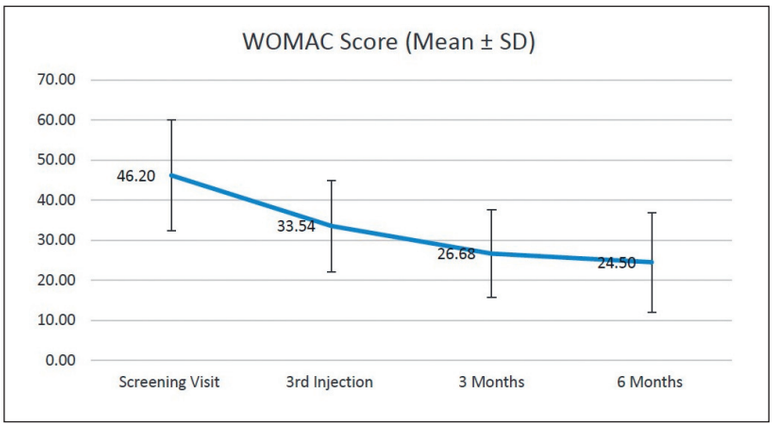

Fig. 1. Total Western Ontario and McMaster Universities osteoarthritis (WOMAC) score (Per-Protocol Population).

The current study aimed to investigate the safety and efficacy of three times application of 20 mg HA with one week interval which is in 2 ml prefilled syringe, in patients with osteoarthritis of knee. Additionally, other questions of the current study were i) whether body mass index (BMI) of the patients affect the outcomes, ii) will outcomes differ among the physicians? and iii) will the grade of the osteoarthritis change the clinical outcomes?

MATERIAL AND METHODS

After ethic committee approval was obtained for the study, patients were enrolled and followed prospectively. Written informed consent was obtained from all patients.

A sample size of 51 achieves 90% power to detect a mean of paired differences of 7.0 with an estimated standard deviation of differences of 15.0 and with a significance level (alpha) of 0.05 using a two-sided paired t-test. It was expected that 20 % of patients will not follow mentioned examination schedule in this protocol; so considering 20% dropout rate around 63 numbers of subjects were required to enroll in the study to have enough data for statistical analysis.

The target population for this study included middle and advanced aged patients and radiologically grade II and III osteoarthritis of knee according to Kellgren and Lawrence classification. Patients who had diagnosis of gonarthrosis according to clinical and radiological evaluation, were given NSAID treatment for four weeks. Patients between 45–80 years old in both sexes, whose pain did not relieve were included to the study and were followed up for 6 months. Patients with secondary osteoarthritis, rheumatologic co-morbidities and taking additional non-operative treatment, previous intra-articular injection (in the past 6 months) were excluded from the study.

HA injections were applied three times with one week of interval. Two orthopedic surgeons (physician A and physician B) performed the injections with standard technique. After gathering the patients' demographic details and baseline clinical and radiological examination, they were evaluated additional three times during the study. Firstly at third week (at the control visit of third injection), secondly at third month and lastly at sixth month. Before application and at the follow up visits patients' clinical evaluation was done by Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index and Short Form Health Survey questionnaire (SF-36) scores. Fulfillment of the scores were done by clinical secretariat who did not attend into the study.

The SF-36 is health status measure questionnaire which is designed to capture in many different conditions (13). The SF-36 includes 36 items and there are eight scales covering the dimensions physical functioning, role limitations due to physical function, bodily pain, general health, mental health, role limitations due to emotional health, social functioning, and vitality and an additional item pertains to health transition. The scores are captured as a 0–100 scale, with higher scores demonstrating better health. These scores are Z-transformed and weighted to yield values used to calculate Physical (PCS) and Mental Component Summary (MCS) scores (13). SF-36 has showed reliability, validity and responsiveness to change in patients with rheumatoid arthritis (13).

Statistical analyses were performed using SPSS Version 21.0 (SPSS, Chicago, IL, USA). In all analyses, $p < 0.05$ indicated statistical significance. Analyzed data were normally distributed. So we compared data before and after needling using paired-samples Student's t-tests and analyzed differences between groups (physician A and B) using independent-samples Student's t-tests. Bi-variate correlations were analyzed using Pearson correlation test.

RESULTS

As 63 patients were enrolled at baseline visit, 56 patients completed the study. Seven patients were excluded because of discontinuity. When power analysis is calculated with 56 patients regarding the differences between

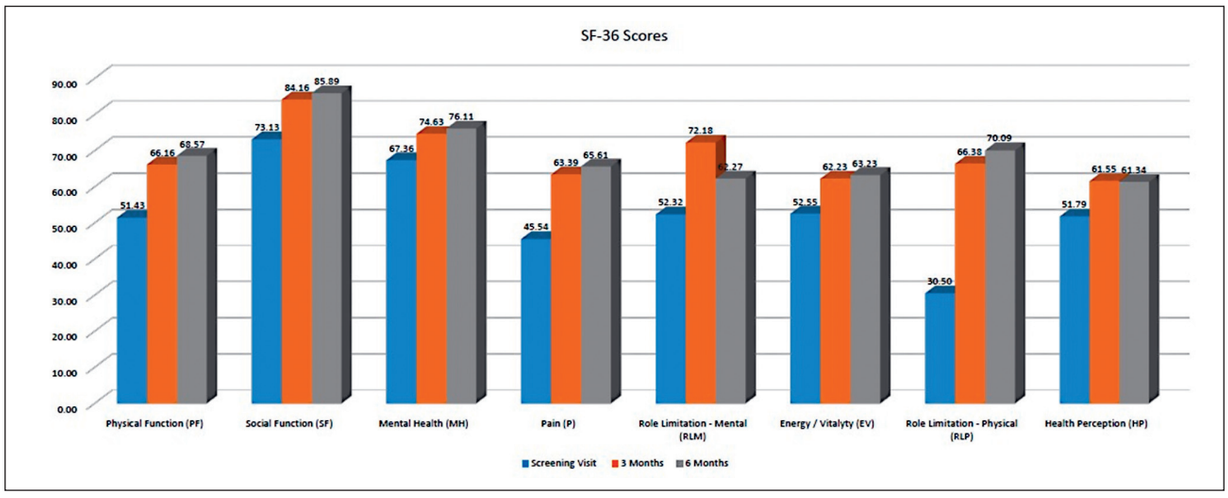

Fig. 2. Mean change in Short Form Health Survey (SF-36) score (Per-Protocol Population).

variables and standard deviations of WOMAC scores it is found that the study had been conducted with 80% power and 0.05 alpha error.

The mean age of the patients was 63.6 ± 6.90 (range 47 and 76) years old. 22 (39.2%) of the patients were male and 34 (60.7%) were female.

BMI of the patients were 30.8 ± 5.4 (range 20.2 and 46.4). BMI and age were significantly related (Pearson correlation test, $p = 0.02$). However; both data before application and at last control, there were no significant relationship between WOMAC scores and BMI ($p = 0.998$ and 0.738 respectively).

Physician A applied injections to 33 patients (99 injections) and physician B applied to 23 patients (69 injections). There were no significant differences between physicians regarding their consideration of treatment. It has been analyzed using Students' t-test. At first application physicians' determination to perform an injection according to radiologic classification was not different ($p = 0.424$). Determining to perform an injection according to WOMAC score was not different ($p = 0.468$). Additionally; at last control visit, patients' clinical evaluation was not differed between two physicians ($p = 0.496$).

The mean radiologic grade of the osteoarthritis was 2.5 ± 0.50 (range 2 and 3). Using Pearson correlation test it was found that there was no significant correlation between radiologic grade and WOMAC scores.

The efficacy of the intra-articular 20 mg/2 ml HA injection were analyzed using Students' t-test. It is found that the treatment method was significantly effective in third and sixth months. WOMAC scores gradually decreased within time (Fig. 1) and at the last control the injections obtained 46.7 % of decrease at the pain due to the gonarthrosis, comparing with the first application ($p < 0.01$). According to one sample t test, the WOMAC scores in sixth month were significantly better than the scores in third months ($p < 0.01$).

Eight scales of SF-36 captured at baseline, 3 months and 6 months follow-ups were analyzed using Student's t-test and Fig. 2 shows the scores per each visit. All eight SF-36 scales were increased at statistically significant ($p < 0.0001$) at 3 month and 6-month follow-up visits.

DISCUSSION

This is a prospective study which indicated the safety and efficacy of the intra-articular 20 mg/2 ml HA injection at the cohort of patients with grade II and III knee osteoarthritis. Strong parts of the study were i) prospective design, ii) statistically enough number of patients and iii) gathering the clinical and radiological data by secretariat of the department who did not attend to the study. On the other hand, the limitation of the study is not having a control group.

The reduction in WOMAC score was higher at 6-month follow-up when compared to 3-months follow-up, which was also statistically significant implying continuing benefit beyond three months. Similar findings have been reported by other authors with respect to improvement in WOMAC score after intra-articular HA injection. In a study by Berenbaum et al, 3-weekly injections of intermediate molecular weight HA in patients with gonarthrosis, mean WOMAC pain score decreased by 22.9±1.4 at the end of 6 months (5). Improvement in WOMAC pain and physical function scores have also been reported in meta-analysis by Bannuru et al. (2) and Bellamy et al. (4). An article which indicates very similar outcomes with our study depicts significant decrease in visual analogue scale and WOMAC over time in treated groups (with intra-articular hyaluronic acid) independently of the radiological grade (9).

As gonarthrosis considerably decreases quality of life, we also assessed change in quality of life with SF-36 in our study. It was observed that all 8 parameters of SF-36 (i.e., physical function, social function, mental health, pain, role limitation-mental, energy/vitality, role limitation-physical and health perceptions) showed significant improvement at 6-months of follow-up. Quality

of life has also been assessed by other studies reported in literature. In a multi-center, open-label study, quality of life was assessed after single intra-articular injection of HA in gonarthrosis. Quality of life was measured by three parameters: Impact on walking, impact on working and impact on sleep. At the end of study (240 days), there was significant improvement in all. three parameters of quality of life indicating positive correlation for the efficacy of the product to improve the quality of life (3). In another similar study by Estades-Rubio et al. indicated that patients had improved in WOMAC scores so there was less need for additional analgesia (12).

There is no consensus for the application of HA in the literature. The dosages and application times may differ according to physicians' choice. In an open label trail by Lee et al., three versus 5 injections of intra-articular hyaluronic acid were compared and it was found that no significant difference between groups in weight bearing VAS, WOMAC, or adverse events (14). In a recent systematic review and meta-analysis compared the pooled effect of single versus multiple injections of HA versus saline injections, found improved outcomes at 3 and 6 months from studies involving 2 to 4 injections compared with 5 injections or more events (8).

Apart from the efficacy and improvement in quality of life, intra-articular HA was found to be safe treatment option as none of the patient reported any adverse event in our study. In a meta-analysis conducted by O'Hanlon et al., authors reported no significant risk of adverse events with intra-articular HA compared to placebo overall as well as local joint (16). Intra-articular HA is generally considered to be a safer alternative to oral NSAIDs and opioids for knee OA. A detailed exploration of its safety was undertaken in a recent systematic review and network meta-analysis of 74 studies of 18 HA products involving 13,042 patients aged 45–75 years which found a very low incidence of adverse events. The most commonly reported adverse events were transient local reactions such as pain, swelling and arthralgia (incidence 8.5%), which subsided rapidly. None of the HA products were statistically significantly different from placebo, nor from each other with regard to incidence of adverse events (16).

In this study our questions waiting for an answer was "whether BMI of the patients affect the outcomes", "will outcomes change according to the physician" and "will outcomes change according to the grade of the osteoarthritis?". We found no relationship in our cohort.

CONCLUSIONS

In conclusion, these results may be interpreted as, independent from the radiologic grade and independent from the physician, use of 20 mg HA injections give satisfactory palliation in gonarthrosis. Injections were effective in improving the WOMAC index and SF-36 scores in patients of knee OA. None of the patient reported any of the adverse events during the study. Overall, the 20 mg/2 ml HA injection can be considered as a good and safe treatment option for the knee OA in patients who do not respond to non-pharmacological therapy, NSAIDs or analgesic.

Institutional Review Board approval was obtained (from İstanbul Medeniyet Universitesi, Goztepe Training and Research Hospital, Clinical Trails Ethics Committee, 23rd January 2018, Approval Number: 2017/0372) for the study. The study was carried out in İstanbul Medeniyet University Göztepe Training and Research Hospital Orthopaedics and Traumatology Department.

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