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Efficacy of Intra-Articular Injection of Hyaluronic Acid in the Treatment of Knee Osteoarthritis

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ABSTRACT

This study was conducted to evaluate the efficacy of intra-articular injection of hyaluronic acid for the treatment of knee osteoarthritis. Patients with knee osteoarthritis were followed for a period of six months to assess the efficacy of intra-articular injection of hyaluronic acid given three times in three consecutive weeks. Fifty patients were reviewed at two, eight and 24 weeks post-injection. The average age was 60.9 years and female to male ratio was 3:1. Patients were assessed using the Lequesne Algofunctional Index for function, and the visual analogue score for pain and side effects. We found that the knee pain reduced and the function improved in most patients and these beneficial effects maintain till the last follow up. The only side effect noted was one case of acute non-septic joint effusion after the 3rd injection. We concluded that intra-articular injection of hyaluronic acid can produce pain relief and functional improvement for up to 6 months.

INTRODUCTION

Osteoarthritis the most common form of joint disease and the leading cause of disability in older adults [1], is characterized by progressive loss of articular cartilage, marginal new bone formation, pain aggravated by activity and stiffness after a period of immobility. The underlying cause is multifactorial with several predisposing factors such as mechanical trauma, obesity, genetic factors, inflammatory joint disease, previous joint infection, advancing age, metabolic factors, osteoporosis and ligamentous laxity. Age is the most important predictive risk factor as osteoarthritis affects people mostly over the age of 60y.

The commonly involved joints in osteoarthritis are the knee, hip, ankle, spine, metacarpophalangeal and the interphalangeal joints. In the knee, pain is usually the presenting symptom followed by progressive loss of motion, joint tenderness, and stiffness, and in the later stages, joint deformity. Less than 50% of patients with radiological changes of osteoarthritis have symptoms of pain [2]; therefore, treatment is based on the symptoms rather than radiological changes. The symptoms of osteoarthritis are mainly localized to the joint involved since it is not a systemic disease, but it can either be unilateral or bilateral.

The mainstay of treatment for early or mild osteoarthritis includes pain relief with non-steroidal anti-inflammatory drugs (NSAIDs), activity modification and physiotherapy. This treatment regime is usually continued until the patients' symptoms worsen to the point that he or she warrants reconstructive surgery such as total knee arthroplasty [3]. Recently there have been reports that some drugs can modify the disease process, provide pain relief and slow down degenerative changes in the joint. Examples of these new drugs are glucosamine sulfate, chondroitin sulfate and hyaluronan [4]. Intra-articular injection of hyaluronic acid has progressively gained popularity over oral medications where oral drug allergy, adverse effects and intake compliance issues are of concern. The objective of this study was to evaluate the efficacy of intra-articular injection of hyaluronic acid for the treatment of knee osteoarthritis.

MATERIALS AND METHODS

Study subjects criteria included: age 35years or older with primary osteoarthritis according to the America College of Rheumatology (ACR) [1986] criteria for classification of idiopathic osteoarthritis of the knee [5]. All subjects had radiological evidence of osteoarthritis of grade 2 or 3 severity according to Kellgren-Lawrence classification, baseline pain score on visual analogue scale (VAS) more than 40 and less than 90 and were able to tolerate treatment with acetaminophen as rescue medication. Patients with diabetes mellitus, ischemic heart disease and hypertension were not excluded. Exclusion criteria included secondary osteoarthritis, recent intra articular injection of steroid (within 3 months prior to the study), bronchial asthma with prolonged steroid intake and bony surgery to the knee (corrective osteotomy). Patients with inflammatory arthritis such as rheumatoid arthritis, systemic lupus erythrematosus (SLE), polymyositis, mixed connective tissue disease (MCTD), gout, or recurrent pseudo-gout were also excluded. After agreeing to undergo intra-articular injection, study subjects were asked to stop all analgesics (except for acetaminophen as necessary) two weeks prior to injection.

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On the morning of the first injection, physical examination was performed to assess for laxity, presence of crepitus, deformity and range of motion. Height and weight of the patients was also recorded to generate the body mass index (BMI). Pain severity was assessed using VAS for pain on standing (for the previous 24 hours) and pain after a 30 metre walk. Functional limitation was assessed again using Lequesne algofunctional index. Radiographs were repeated with Rosenberg weight bearing view to document the severity of the knee osteoarthritis according to the Kellgren-Lawrence grading system [6]. Written informed consent was obtained from all study subjects, and all were informed that they may opt out from this study at any time.

Intra-articular injection of hyaluronic acid (Synocrom, Syno-Vital) was used in this study. Hyaluronic acid is a long, unbranched polysaccharide chain. The injection was given 3 times at one-week intervals. Patients were also prescribed 'rescue analgesia' of acetaminophen to a maximum dose of 4gm a day.

Patients were then followed-up at 2, 8 and 24 weeks after the last injection. No rescue medication was allowed from midnight of the day before clinical review for each appointment. Compliance with prescribed study medications was determined by asking the patients about the quantity and type of rescue analgesia used. No other drugs for osteoarthritis were allowed during this period. After 6 months of follow-up all the data were then analyzed using statistical software (SPSS, Version 12 for Windows).

RESULTS

Fifty-six patients were recruited for the study. The mean age was 60.6 years (range 37 to 83 years). There were 15 males and 41 females (male: female ratio was 1 to 3). Symptoms was present between five and ten years for 42.9% of the patients. On radiological evaluation, 30 patients (53.6%) were noted to have grade 3, while 26 patients (46.4%) had grade 2 osteoarthritis. Most patients did not have normal body weight. Fifty per cent were overweight, 25% were obese and 3.6 % were morbidly obese according to their calculated BMI (Figure 1).

Fifty of the fifty-six patients were available for evaluation at the end of six months. Two patients opted out at the first follow-up, two on the subsequent and two more on the last follow up at 24 weeks. In total, this amounted contributed to a dropout rate of 10.5%.

Pain, assessed by use of the visual analogue score (VAS), revealed an average pain score of 6.96 pre-injection for standing during the previous 24 hours and 8.28 for walking 30m. From this base line, the value dropped to 5.77 and 7.04 respectively at 2 weeks after the third injection. There was continuous improvement, with the value at 4.00 and 5.13 at the 8th week, and 3.58 and 4.71 at the last follow-up at 24 weeks. The basic pattern of change was similar to that of the Lequesne algofunctional index (Figure 2). A paired t- test performed for periods between pre-injection and second week, eighth week and 24th week showed significant statistical differences. Between zero and two weeks, the mean was 1.19 (SD 1.36); between zero and eighth weeks the mean was 2.96 (SD 1.82), and lastly between zero and 24 weeks the mean was 3.39 (SD 2.18) ($p< 0.01$for all comparisons).

During the first two weeks, assessment for standing showed that 40 out of 54 (74%) had improvement, 13 out of 54 (24%) remained unchanged and one out of 54 (1.8%) worsened. Between second and eights week standing assessment revealed that 44 out of 52 (84.6 %) improved, six out of 52 (11.5%) remained static and two out of 52 (3.8%) worsened. Lastly, between the 8th and 24th week, assessment for standing showed that 22 out of 52 (42.3%) improved, 20 out of 52 (38.4%) remained static and 10 out of 52 (19.2 %) worsened (Figure 3).

For walking 30m, 43 out of 52 (82.6%) improved, while nine out of 52 (17.3 %) remained the same at two weeks after the last injection. Between the second and eighth week, 38 out of 54 (70.3%) improved, 14 out of 54 (25.9%) remained unchanged and one worsened. Then, between the eighth and 24th week, walking 30m revealed that 19 out of 52 (36.5%) improved, 22out of 52 (42.3 %) remained static and 11 out of 52 (21.1%) worsened (Figure 4).

Based on the mean value of the Lequesne algofunctional index for the whole group, we could see a gradual improvement in function from pre-injection to 2, 8 and 24 weeks post-injection At pre-injection, the mean Lequesne index score was 10.38 points, at two weeks it was 9.32 points, at eight weeks, it was 7.27 points and at 24 weeks it was 6.84 points. Overall improvement at the last follow up was 34.5% ($p<0.01$) compared to the pre-injection value. We also noted that at eight weeks the improvement was already in the region of 3.3 points, corresponding to a 30% improvement ($p<0.01$). This observation indicated that functional improvement mainly occurred within the first 8 weeks (Figure 5 & 6).

One case was complicated by non-septic acute knee effusion, which mimics septic arthritis. This particular patient developed knee swelling about a week after the third injection. The patient recovered uneventfully with only analgesics and anti-inflammatory medications.

DISCUSSION

Pain was the single most important reason for the patients to seek medical attention for their knee problems. Activity-related discomfort led to variable timing of presentation of

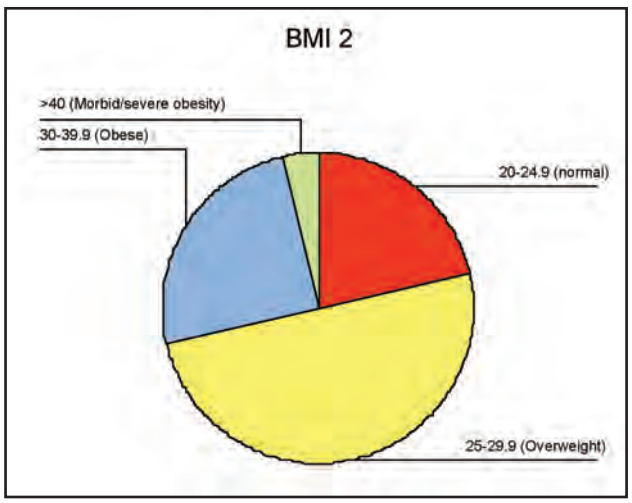

Fig. 1: Distribution of obesity in patients with knee osteoarthritis.

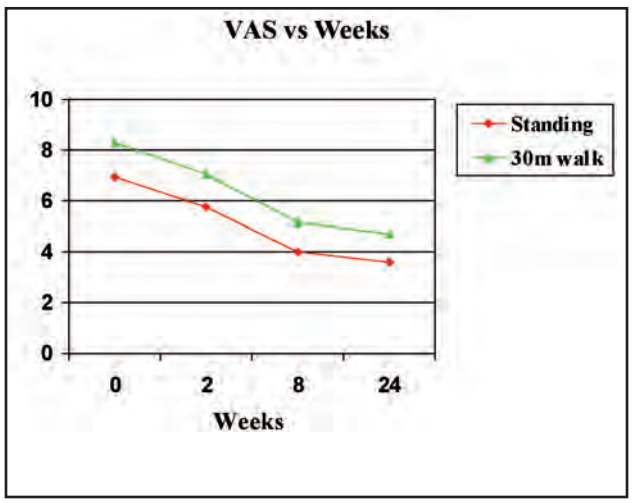

Fig. 2: Mean VAS score over the duration of follow-up.

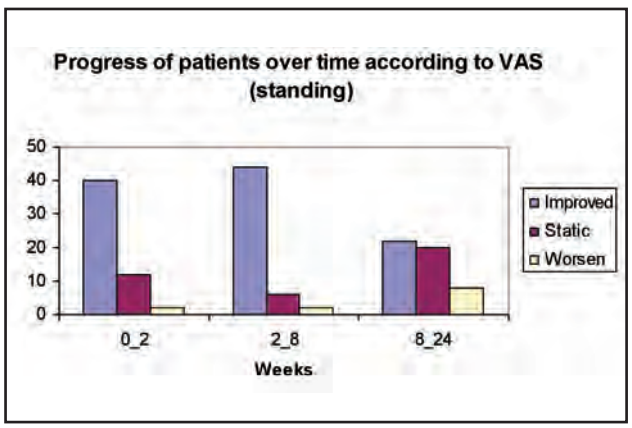

Fig. 3: Progress of patients over time according to VAS (standing).

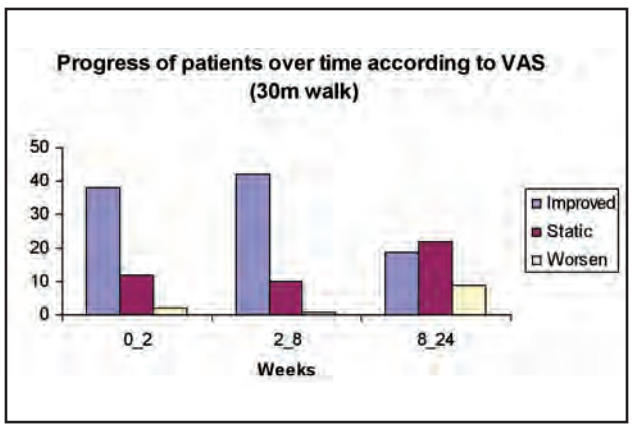

Fig. 4: Progress of patients over time according to VAS (30 m walk).

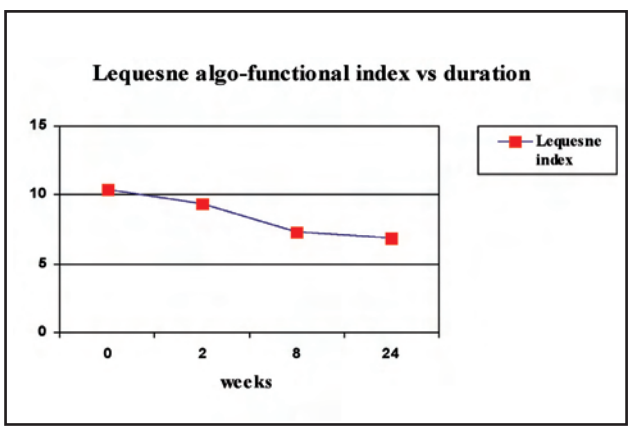

Fig. 5: Lequesne algofunctional index according to the duration of follow-up.

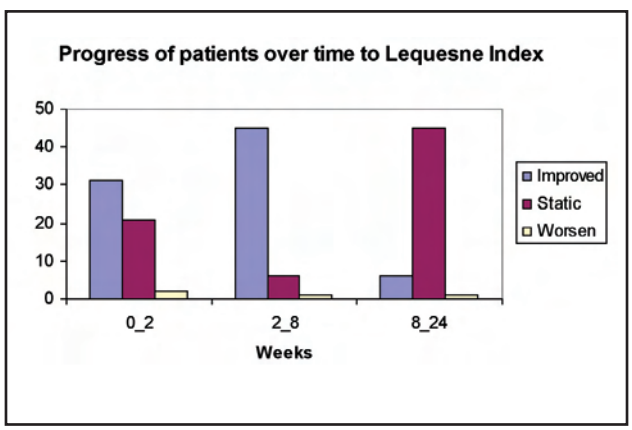

Fig. 6: Progress of patients over the six months.

these patients for medical treatment. There is of course variation in each individual's pain threshold. Some are able to withstand pain for longer duration than others. The VAS values also showed gradual but significant improvement in terms of pain at rest or after a 30m walk with the most significant improvement recorded at the second follow-up (8 weeks following the third injection). Thereafter, a large group of the patients experienced sustained pain relief till the end of twenty-four weeks. A small number of study subjects started developing pain similar to pre-injection discomfort and corresponding deterioration in pain scores.

Obesity is closely related to the overall picture of these patients either having osteoarthritis in the first place as well as to the effectiveness of the treatment regime [7]. Many patients tend to state that family history as the reason for their obesity and a significant number attribute progressive increase in weight to activity restriction [8]. We observed a gradual decrease in the usage of escape drugs in the course of the treatment. The escape medication in this study was acetaminophen.

It should be noted that hyaluronic acid injections can play a role in early management of osteoarthritis especially for those with allergies to glucosamine and also those with severe gastrointestinal tract disorders secondary to NSAIDS. At the other extreme, are the surgical candidates for knee replacement who are sadly not fit for surgery, so would require intra-articular injections for symptomatic relief. Patients who benefited most from these injections were those with early, mild to moderate osteoarthritis. We believe that a treatment regime of three injections resulted in satisfactory outcomes in the current study but there is still room for improvement in the formula of the hyaluronic preparation, duration of regime and perhaps also in the technique for administering the injection. Lequesne defined effective treatment as those leading to a 30-40% improvement in score at time of follow-up [9]. The reduction of Lequesne score for the current study following treatment (from 10.38 to 6.84) points represents an improvement of 34.5%, and is thus defined as effective.

The limitation of this study is the inability to exclude the placebo effect of this injection as there is no comparative arm involved; further, a longer duration follow up would provide more information on the long term functional outcome. Finally, there is a possibility of recruitment bias since the study was based on a single institution.

CONCLUSION

The results of this study showed that a regime of three intra-articular injection of hyaluronic acid administered in three consecutive weeks has a significant effect on functional outcome and reduction of osteoarthritic knee pain for at least six months.

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