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# Comparison between Four Types of Single-Dose Hyaluronic Acid Injection in Patients with Knee Osteoarthritis: A Randomized Control Trial

*Hafez MA*, Askar M, Nabeel A, Hassan KO and Khalifa AMS*

*Department of Orthopaedics, October 6 University, Cairo, Egypt*

## Abstract

**Aim:** Evaluating and comparing 4 types of hyaluronic acid used as intra-articular injection for knee osteoarthritis in view of their clinical outcome and cost.

**Methods:** Total of 156 patients with knee osteoarthritis was recruited. All patients had grade II-III Kellgren and Lawrence grading scale OA. Patients were randomly divided into 2 groups (low cost and high cost). The used gels were Monovisc, Crespin plus (high cost) and Intragel, Crespin (low cost). Lower extremity function scale (LEFS) was measured for all patients before injection and 6 and 12 months post-injection; and visual analogue scale (VAS) was reported at baseline and 6 months after injection.

**Results:** At 6 months, LEFS value for Intragel was 9, for Crespin 6.9, for Crespin plus 8.15 and for Monovisc 11.4; while VAS value for Intragel was 2.9, for Crespin 1.86, for Crespin plus 4.5 and for Monosvisc 4.12. At 12 months, LEFS value for Intragel was 10.6, for Crespin 19.9 and for Monosvisc 23.3.

**Conclusion:** There was an overall increase in LEFS values and decrease in VAS values indicating the good therapeutic effect of the four drugs with no statistically significant difference between the low cost and the high cost.

**Keywords: Hyaluronic acid; Intra-articular injection; Monovisc; Crespin plus; Intragel; Crespin**

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***Correspondence:***
*Mahmoud A. Hafez, Department of Orthopaedics, Al Helal National Orthopaedic Hospital, October 6 University, Cairo, Egypt, Tel: +201007566299;*
*E-mail: mhafez@msn.com*

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## Introduction

Osteoarthritis (OA) is a chronic, slowly progressive, erosive damage of joint surfaces which leads to loss of articular cartilage and causes increasing joint pain and failure [1]. Non-operative management of knee OA includes oral chondroprotective drugs and intra-articular injections, such as hyaluronic acid (also known as hyaluronan), corticosteroids and platelet rich plasma [2].

Hyaluronic acid (HA) is a natural ingredient of extracellular matrix that has been routinely used to replace cartilage. It possesses high stability and wetting properties through stabilizing aggrecan compounds and retaining water, while resisting swelling, at the site of injection. However, its effect is dependent on the administered dose and concentration [3]. It is readily contained into the synovial fluid of the joints but in variable quantities and forms which could be analyzed with chromatography, fluoroscopy, electrophoresis or radiometry; however, none of these have been known as a validate method for such analysis [4].

HA is prescribed either in single or in multiple intra-articular injections. Its viscosupplementation has a wide usage, thanks for its capability to replace minimized HA and to relief pain [2,5]. Single-injection hyaluronic acids were found to have comparable effect to multiple-injection counterparts in terms of pain relief and functional improvement but significantly lower rate of side effects [4].

In comparison to intra-articular corticosteroids, HA was found to last longer with less serious long-term complications. In addition, intra-articular HA (IAHA) is safer than NSAIDs, especially when their adverse effects become intolerable [6]. It works on slowing down the pathological process of OA through its chondroprotective and lubricating nature that aids in stabilizing joint cartilage and synovium as well as its anti-inflammatory, analgesic effect that helps in pain management and improving joint status [6]. However, there is no consensus supporting the use of a particular composition of HA over the others [7]. The cost of HA injection is relatively high and there is

also variations in the cost between its different types. No available information in the literature about the effectiveness of the cost of injection.

The aim of this work is to evaluate the clinical outcome and to compare between 4 types of intra-articular injection of HA for knee OA in view of their cost.

## Patients and Methods

This is a randomized, single-blinded clinical study. A number of 156 patients (age 20–70 years, average 45 years; male to female ratio 1:5) with knee OA between grades II and III according to Kellgren and Lawrence grading scale were included. Written consents were obtained from all patients to be involved in this study. All patients had no higher-grade arthritis in other joints. Exclusion criteria were severe knee OA that requires surgical intervention, patients with immunity suppression, active inflammatory state, infection, bleeding tendency, anticoagulant therapy, known allergy to HA and patients who refused injection and declined participation in the study were excluded.

Four types of HA were used for this study: Monovisc, Crespin plus, Intragel and Crespin. These drugs all contain cross linked hyaluronic acid salt at varying concentrations (14 mg, 14 mg, 16 mg and 22 mg, resp.). Although Crespin and Crespin plus have the same concentration, they differ that Crespin contains 6.9 mg of sodium chloride while Crespin plus contains 3 mg of prilocaine.

Patients were randomly divided in to two groups: group I included Crespin and Intragel (low-cost injections), and group II included Crespin plus and Monovisc (high-cost injections).

Patients' economic status was considered in randomization, that is, group I injections were less expensive than group II (almost half price). Initially, patients falling into low- or high-cost group was based on affordability, then patients in each group were randomized to either one of the two HA injections.

Patients were assessed to test their lower extremity function scale (LEFS) and visual analogue scale (VAS) to determine the outcome of injection. All patients were prescribed a generic analgesic, were advised to consume one tablet whenever they experience any pain and were asked to record the frequency of analgesics intake in order record it in a case-series form.

The patients were divided upon the 4 HA types as follows: 43 for Intragel, 64 for Crespin, 32 for Crespin plus and 17 for Monovisc. The mean Kellgren and Lawrence grading scale was recorded at baseline as 2.72 for the Intragel group, 2.64 for the Crespin group, 2.52 for the Crespin plus group and 2.18 for the Monovisc group.

The baseline LEFS for the patients under all control groups before HA administration indicated the following levels: 34.6 for the Intragel group, 31.8 for the Crespin group, 27.9 for the Crespin plus group and 39.2 for the Monovisc group.

The baseline VAS under all control groups indicated as follows: 7.01 for the Intragel group, 6.32 for the Crespin, 7.25 for the Crespin plus and 7.12 for the Monovisc group (Table 1 and 2).

## Results

The LEFS values recorded at 6 months expressed the following values: 43.6 for the Intragel group, 38.7 for the Crespin group, 36.05 for the Crespin plus group and 50.6 for the Monovisc group. The

**Table 1:** The baseline values of Kellgren and Lawrence grading, LEFS and VAS.

| Patient Baseline Values | Intragel | Crespin | Crespin plus | Monovisc |
|---|---|---|---|---|
| O.A Grade | 2.72 | 2.64 | 2.52 | 2.18 |
| VAS | 7.01 | 6.32 | 7.25 | 7.12 |
| LEFS | 34.6 | 31.8 | 27.9 | 39.2 |

**Table 2:** The overall improvement of LEFS and VAS scores.

| Overall Average Results | INTRAGEL | CRESPIN | CRESPIN PLUS | MONOVISC |
|---|---|---|---|---|
| LEFS Increase At 6 Months | 9 | 6.9 | 8.15 | 11.4 |
| LEFS Increase At 1 Year | 10.6 | 19.9 | N/A | 23.3 |
| VAS Decrease At 6 Months | 2.9 | 1.86 | 4.5 | 4.12 |

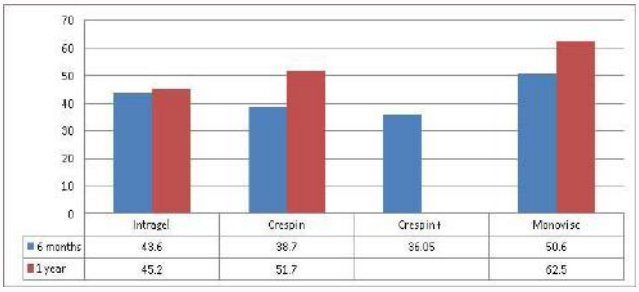


**Figure 1:** LEFS results in 6 and 12 months.

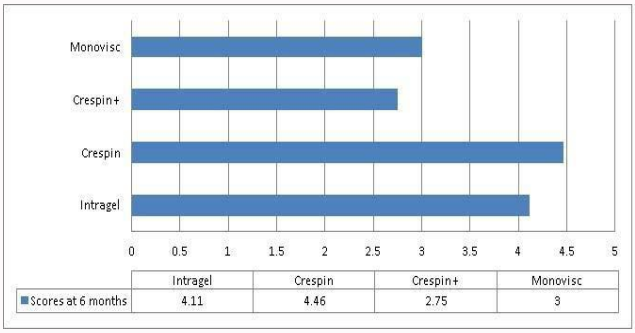


**Figure 2:** VAS results in 6 months.

LEFS values recorded after 1 year showed 45.2 for the Intragel group, 51.7 for the Crespin group and 62.5 for the Monovisc group (Figure 1).

The VAS values at 6 months were 4.11 for the Intragel group, 4.46 for the Crespin group, 2.75 for the Crespin plus group and 3 for the Monovisc group (Figure 2).

To compare the 4 HA variations, the focus was on the resulting differences in relation to the target parameters used, namely, LEFS and VAS scales. Average LEFS scores over 6 months showed an increase by 9 scores for Intragel, 6.9 for Crespin, 8.15 for Crespin plus and 11.4 for Monovisc. The same scores over 1 year showed an increase by 19.9 for Crespin, 10.6 for Intragel and 23.3 for Monovisc. VAS score decreased over 6 months by 2.9 for Intragel, 1.86 for Crespin, 4.5 for Crespin plus and 4.12 for Monovisc.

In the low-cost group, Intragel expressed a higher LEFS value at 6 months while Crespin expressed a higher value at 1 year. Intragel demonstrated better VAS results compared to Crespin. In the high-cost group, Monovisc LEFS results showed the highest overall increase at 6 months while Crespin plus had the best overall VAS reduction.

The visual analogue scale showed a marked difference between the two groups with a 23.5% and 43% scale reduction for both low-cost and high-cost groups, respectively.

## Discussion

To the authors' knowledge, no studies in literature have found that HA injections have significant adverse effects in their trials, and no significant side-effects were observed other than the general complaint of joint stiffness and post-injection pain which disappear spontaneously within a week without any intervention and with no limitations on the patient's daily activities. Any side-effect or adverse effect, such as pain or swelling, could have a higher potential with the use of high-molecular-weight IAHA injections [8].

IAHA injections were found to have major therapeutic effects on pain and function between 4 and 26 weeks, and these effects are prolonged for up to 18 months and become more efficient than corticosteroids after 8-week margin [7]. A level-one-evidence, comparative study on hyaluronic acid and corticosteroids concluded that HA has more stable therapeutic effects up to 26 weeks [9]. In comparison to platelet-rich plasma (PRP), HA has proven to be greater in therapeutic effect and thus recommended as a first line of treatment [10].

No previous studies in literature have compared the effects of four different types of hyaluronic acid. The data presented here in showed an overall patients' satisfaction and improved lifestyle. In addition, the method of randomization with high-cost or low-cost medication did not comprise any financial stress for patients and offered some psychological comfort. General information about the used medications is summarized as follows.

Crespine (for each 1 mL) contained 14 mg of cross-linked hyaluronic acid sodium salt, 6.9 mg NaCl and water for injection; it was administered as one single injection. Intragel (for each 1 ml) contained 16 mg hyaluronic acid sodium salt; it was administered as two ampules. Crespine plus (for each 1 ml) contained 14 mg sodium hyaluronate, cross-linked 1 mg sodium hyaluronate, 3 mg prilocaine and water for injection; it was administered as one single injection. Monovisc (for each 1 ml) contained 22 mg lightly cross-linked sodium hyaluronate dissolved in phosphate-buffered saline at physiological osmolality; it was administered in a single injection.

The four drugs are generally indicated for correcting joints with degenerated articular surfaces, altered synovial fluid, reduced mobility and pain. Their general contraindications are among altered immunity, active inflammation, infection or skin rash especially at the site of injection, patients on regular anticoagulant therapy and patients with known allergy to HA or blood disorder. Their side-effects are between temporary erythema, slight swelling, and mild-to-moderate episodes of transient pain, itching, discoloration and hardening at the injection site. The four drugs could be stored at room temperature.

IAHA injections were found to be more beneficial for patients with low Kellgren and Lawrence grading scales (i.e., I and II) [11]. This claim was supported by a comparative study on IAHA injections with mean reduction of 43.8% and 33.1% improvement in JKOM scores across Kellgren and Lawrence grading scales I and II, respectively. In another study, IAHA had a mean reduction of 41.2% in VAS score, which is clinically significant for Kellgren and Lawrence grading scales I and II [12]. In addition, the use of analgesics was substantially reduced after IAHA viscosupplementation; and a significantly lowered Lequesne index from abaseline of 5.9 to 3.1 and 2.6 after 6 and 12 months, respectively, by IAHA injection was reported [13].

The AMELIA project highlighted multiple injections of HA and reported a 20% reduction in overall pain score in 79.2% of patients and a 50% reduction in overall pain and function in 65.1% of patients [14].The results of another multiple-injection study showed pain reduction ranged from 28% to 54% [5]. In light of single IAHA, the overall pain reduction was found to be33% by VAS, which could even exceed the minimum significant reduction (25%) which denotes its worthy clinical effect [15].

These results are in accordance with our findings on the overall improvement of function with a 9 point average increase in LEFS in relation to the mean Kellgren and Lawrence grading scale of 2.5. This work shows that all 4 drugs used for IAHA had a moderate clinical effect on knee OA that lasts for up to 12 months. In our study, the most noticeable outcome is pain reduction which had reached 43% in the Crespin plus and Monovisc groups, which denotes that single IAHA injections have considerable therapeutic effect. This result is close to the recommended target pain reduction (40%) which was presented by Tubach et al. [16].

The placebo effect in our study cannot be excluded. The absence of significant difference between low- and high-cost injections could be influenced by this placebo effect.

Limitations of this study are 28% of patients were lost for follow up; the number of patients for each group was unequal due to commercial shortage in one of the injections during the period of the study (Monovisc); there was no control group or placebo [17].

## Conclusion

The benefits from a single injection of HA demonstrated a potential to last for up to 12 months among the four control groups. The therapeutic value of HA indicated an overall increase in LEFS values and decrease in VAS values. HA viscosupplementation causes a reduction in pain which allows for a wider range of mobility. There was no statistically significant difference between low- and high-cost injections.

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