Evaluation of the effectiveness of two formulations of hyaluronic acid for knee osteoarthritis.

Rihab Muhammad*, Dania Mustafa, Julinar Mohamed**, Rawia Zayed*****

Pharmacology and Toxicology department, College of pharmacy, Mustansiriyah University, Baghdad, Iraq.

****Baghdad Health Directorate / Al-Karkh Branch / Al-Yarmouk Teaching Hospital, Baghdad, Iraq.***

*****Pharmacognosy department, faculty of pharmacy, zagazig University, Egypt.***

Article Info:

Received 27 Aug 2024
Revised 10 May 2025
Accepted 23 June 2025
Published 31 Dec 2025
Corresponding Author email:
Rihabguaim@gmail.com
Orcid: https://orcid.org/0009-0001-0121-8736

DOI: https://doi.org/10.32947/ajps.v25i5.1252

Abstract:

Hyaluronic acid (HA) is a hydrophilic, negatively charged of glycosaminoglycan polymer which its physiological role, rheological properties, and uses are largely determined by its molecular weight. Hyaluronic acid help joints to work efficiently through providing the needed lubrication, cushioning, and hydration.

The main goal of this study is to compare the efficacy related to cost of two different forms of hyaluronic acid (Arthromac® and monovisc®) in patients with knee osteoarthritis.
In this study, 30 knee osteoarthritis patients suffering from knee osteoarthritis and intense discomforting pain were randomly assigned to receive one of the two formulations of Hyaluronic acid: cross-linked hyaluronic acid plus mannitol (Arthromac®) and natural hyaluronan (monovisc®). Symptoms and function parameters were assessed before and 4 months after injection through Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The results revealed that both Arthromac® and monovisc® decreased the WOMAC score of the pain, stiffness, and physical function compared to before use. However, once comparing them, there is no difference between Arthromac® and monovisc® in terms of efficacy. and the relative difference between the two is mainly the cost and also the number of doses in the course.

Keyword: hyaluronic acid, knee osteoarthritis, various formulations, cost-Effectiveness

المقارنة بين نوعين من حمض الهيالورونيك من حيث السلامة والفعالية في علاج التهاب المفاصل التنكسي في الركبة.

رحاب محمد*، دانيا مصطفى **، جلنار محمد **، راوية زايد**

قسم علم الأدوية والسموم، كلية الصيدلة، الجامعة المستنصرية، بغداد، العراق

****دائرة صحة بغداد /الكرخ /مستشفى اليرموك التعليمي، بغداد، العراق***

*****قسم العقاقير، كلية الصيدلة، جامعة الزقازيق، مصر***

الخلاصة:

حمض الهيالورونيك : هو بوليمر جليكوساميجليكان محب للماء، مشحون سالبًا، ويتم تحديد دوره الفسيولوجي وخصائصه الريولوجية واستخداماته إلى حد كبير من خلال وزنه الجزيئي. يساعد HA المفاصل على العمل بكفاءة من خلال توفير التشحيم والتوسيد والترطيب اللازمين.

الهدف الرئيسي من هذه الدراسة هو مقارنة الفعالية نسبة الى الكلفة شكلين مختلفين من حمض الهيالورونيك (Arthromac® و monovisc®) في المرضى الذين يعانون من التهاب مفاصل الركبة .

في هذه الدراسة، تم تعيين 30 مريضًا مصابًا بالتهاب المفاصل العظمي في الركبة والذين يعانون من التهاب المفاصل العظمي في الركبة وألم شديد مزعج بشكل عشوائي لتلقي إحدى تركيبتي HA: حمض الهيالورونيك المتشابك بالإضافة إلى مانيتول (Arthromac®) والهيالورونان الطبيعي (monovisc®). تم تقييم الأعراض والمعلمات الوظيفية قبل وبعد 4 أشهر من الحقن من خلال مؤشر هشاشة العظام في جامعات أونتاريو الغربية وماكماستر (WOMAC). كشفت النتائج أن كلا من Arthromac® وmonovisc® قللا من درجة WOMAC للألم والتصلب والوظيفة البدنية مقارنة بما كان عليه قبل الاستخدام. ومع ذلك، بمجرد مقارنتها، لا يوجد فرق بين Arthromac® وmonovisc® من حيث الفعالية. والفرق النسبي بين الاثنين هو في الأساس التكلفة وكذلك عدد الجرعات في الدورة.

الكلمات المفتاحية: حمض الهيالورونيك، التهاب مفاصل الركبة، تركيبات مختلفة، الفعالية الى التكلف.

1.Introduction

Osteoarthritis (OA) is a progressively deteriorating disorder of joints characterised by spontaneous loss of articular cartilage[1]. The cause of OA is not fully understood yet, however pathogenesis is consisting of interconnected parts affected by a variety of biochemical and mechanical factors[2].

Data from the mid-20th century until now has revealed an increase of up to twofold in the prevalence, essentially due to the major rise in both weight and age; in other words, obesity and ageing are considered (along with the high Inflation rate) one of the main reasons as to why it has become quite common in society.

The United Nations Department of Economic and Social Affairs stated that the global population increased from 5.32 billion to 7.71 billion between 1990 and 2019, marking a 45% increase. Over the last few centuries, the human population has gone through an extraordinary change. In 1800, there were one billion people. Today there are more than 8 billion.[3]

In addition, the number of elderly people over 60 increased from 9.2% to 13.5% during the same period. Furthermore, many joint injuries, especially when ligaments are included, have a high probability of resulting in joint degeneration, besides the increase in the awareness and recognition of OA compared with 1990, which also contributed to an increase in OA prevalence[4].

Knee OA is secondary to cardiovascular diseases as a reason for disability (even ability to walk and move up the stairs) in old people.Among adults 60 years of age or older the prevalence of symptomatic knee OA is approximately 10% in men and 13% in women.[5]

considering that the old-age population community is increasing, it is going to be an extremely critical condition. OA has two main categories primary osteoarthritis is either localised or generalised; the latter is mainly seen in post-menopausal women. Secondary osteoarthritis has an underlying cause, like trauma, obesity, Paget's disease, or inflammatory arthritis.[6]

Since a cure for OA does not yet exist, prevention strategies that target these modifiable factors are needed to curb further increases in OA prevalence.[7]Patients, more than 50 years old and above, who suffer from pain and stiffness in the injured joint most

likely would experience severe pain upon doing an activity, which usually could be relieved by rest since rest works well for for most injuries., yet some may experience typical morning stiffness, which may last for a while[8].

The signs of osteoarthritis include: Sharp pain upon moving or touching the affected joint, nodule, or a lump because of distortion as in osteophyte formation or in the form of oedema caused by synovial fluid accumulation.

All these signs could be experienced in OA, but systemic symptoms remain absent, although erythrocyte sedimentation rate may show abnormality.[7&9] Hyaluronic acid (HA) , which could be called hyaluronan or hyaluronate, is a mucilaginous material that is naturally found in humans. In the joints, it serves as a lubricant, helps in the development of cartilage and bone, and may reduce any inflammation.Intra-articular HA therapy provides therapeutic relief through a number of pathways, including the suppression of pro-inflammatory cytokines and chemokines via inhibitors of the signal transduction pathways from specific cell surface receptors, as well as promotion of the synthesis of anti-inflammatory mediators.[7] Evidence has shown that HA oligosaccharides and HMWHA polymer chains bind to cell surface receptors such as cluster determinant 44 (CD44), toll-like receptor 2 (TLR-2) and 4 (TLR-4), layilin (LAYN), and intercellular adhesion molecule-1 (ICAM-1). Since HA has an established impact on inflammation in osteoarthritis.[10]

Considering the fact that the majority of human cells can produce HA, it could be found in different places, such as in the extracellular matrix in bone marrow, cartilage, and synovial fluid in joints. The H.A molecules are predominantly synthesise by type B synoviocytes.[11]

Hyaluronic Acid is mostly obtained from bacterial fermentation or extracted from specific animal tissues, mainly rooster combs, or via recombinant DNA technology (in vitro).[12]

In case of knee OA, the main hallmark is the sharp decline in hyaluronic acid concentration, which leads to decreasing the thickness of synovial fluid, which maintains the joints from excessive friction. Hence the injection of intra-articular hyaluronic acid could enhance the thickness of the synovial fluid again (by stimulate the native synovial sites to produce more hyaluronic acid), eventually lowering the friction andjoint. ately decreasing the discomfort of the injured joint. [13]

The objective of this study is to compare therapeutic efficacy of two hyaluronic acid (Injectable formulations) Arthromac® and monovisc® in patients with knee osteoarthritis before and after the administration.

2. Patients and Methods

2.1. Study design

The trial sets the results within around 16-week. It is a randomized, double-blind study that involve observing the clinical results along with the side effects upon the injection of an isolated intra articular (I.A) injection of HA- monovisc®and an isolated intra articular (I.A) injection of HA- Arthromac® and comparing both formulations in terms of relieving pain as a symptom of knee OA.

2.2. Study area and population of the study

The population that was targeted in this study included Iraqi adult's female and male (25 years or older) visiting the governmental hospitals & private clinics in Baghdad due to Knee OA.

Candidates were selected from the outpatients of four different health center and hospitals in Al-Harthia, Baghdad, Iraq. The

local Ethical Committee of each location along with the Iraqi National Regulatory Authorities (specific national regulation) approved the trial protocol.The study involved five visits in total:

1. Visit 1: screening was done in this visit.
2. Visit 2: a baseline visit that involved the randomization along with administration of I.A. Monovisc or Arthromac.
3. Visit 3: occurred a week after treatment
4. Visit 4: occurred after 8 weeks after treatment
5. Visit 5: occurred after 16 weeks after treatment and served as the last visit and the endpoint of the study.

2.3. Treatments and Randomization

Through computer software, the participants were randomised into two groups (at a ratio of one to one) to inject either Monovisc® or Arthromac®. The injection was injected by a specialist and the clinical situation of the candidates involved was not identical (each was at different OA stage). Objective knee evaluation was done and documented.

The medical tool of non-chemically altered hyaluronic acid (as a salt of sodium) of biofermentation source HA concentration: 88 mg/4 ml monovisc® and non-animal origin HA concentration: 30 mg/ml Arthromac.

The therapies were given by either a specialist or a well-trained physician with proper knowledge in the evaluation and handling of patients with knee OA and intra-articular injection procedures.

The main result was obtained through comparing the changes in pain, stiffness, & physical activity between the first & final visits of the 16 weeks.

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a renowned index used in OA estimation. WOMAC was developed in 1982 by Western Ontario and McMaster Universities. Currently, it is accessible in more than 65 languages.[14&15] WOMAC is available in a self-administered questionnaire that involves 24 elements split into 3 subsidiary scales:

1. Pain (5 items): during walking, climbing stairs, in bed, sitting or lying, and standing upright.
2. Stiffness: early in the morning and during the day
3. Physical Function: as in using stairs, changing positions, bending, getting in/out of a car, putting on/taking off socks, getting in/out of the bath, sitting, movement in the bathroom while using the toilet, Tough daily activities, light domestic choir.

It should be noted that rheumatologists most likely prefer to do blood tests such as Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) for everyone suffering from joint problems rather than questionnaires to evaluate the patients.[16] however in this study questionnaires were used to evaluate the results after the treatment.

3.Results

3.1 Characteristics of patients at inclusion:

Table 3.1 includes the characteristics of the patients before the injection of HA; age, gender, BMI, and WOMAC scores for pain, functions, and stiffness. One could tell that the pain and physical function scores are close in both groups but there is a noticeable difference in the stiffness.In terms of unwanted effects, in some case there was a piercing pain upon injection in addition to risk of sepsis and oedema. Furthermore, one should notice the cost of the two injections as well as the number of doses/courses, Arthromac®is taken as a single injection, while monovisc®is taken in three doses per course. The cost of monovisc®is higher than the Arthromac®as shown in Table 3.1

TABLE 3.1 Characteristics of patients at an inclusion

Characteristics Patience	Arthromac® Group	monovisc® Group	P-value
Age (years)			
Age 40-65	12	11	0.18
Age more than 65	3	4	0.18
Gender %			
Men	40%	40%	1
Women	60%	60%	1
BMI	29.29	30.48	0.38
WOMAC score			
Pain	10.5	11.3	0.185
Stiffness	1.9	3.9	< 0.01*
Activity	11.9	11.6	0.818
Mean cost per patient	240,000IQD	990,000IQD	< 0.0001*

Note: *BMI: body mass index *WOMAC: Western Ontario and McMaster Universities Arthritis Index. * Statistically significant p-value.

3.2. Result of Arthromac and Monovisc

The difference in WOMAC scores before and four months after taking a course of HA in both monovisc®and Arthromac®groups revealed a significant improvement in the scores of pains, stiffness, and physical functions in both groups, as follows:

- Pain score: Arthromac®reduces the pain from around 10.5 to 5.8 on the scale, while monovisc®lowers the pain which was 11.3 before injection, to around 5.7 after the course of treatment, showing that Arthromac® (4.7) is a better choice to relieve pain than monovisc® (5.6)
- stiffness score: Arthromac®decreased the stiffness (1.9) to 1, while, on the other hand, monovisc® changed the score from 3.9 to almost 2.2 suggesting a stronger activity & being the preferable over Arthromac®for severe stiffness.
- Physical Activity: Arthromac® (11.9 to 5.5) & monovisc® (11.6 to 5.2) both reduce the disability by around half.

Both of the IA injections with HMW-HA were co-occurred with a sharp pain or slight knee oedema in some patients.However, the percent of WOMAC scores reduction does not differ significantly between monovisc®and Arthromac®groups, as seen in Table 3.2.

TABLE 3.2 Difference between Arthromac®and monovisc®according to WOMAC score.

Group		Womac score "pain "			P value (Arthromac® vs. Monovisc®)	
		M0	M4	P value	baseline	Post treatment
Arthromac®	Mean	10.5	5.7	< 0.0001****	0.185	0.17
	SD	1.12	2.4			
monovisc®	Mean	11.3	5.26	< 0.0001****		
	SD	1.98	2.37			

Group		Womac score "stifness "			P value (Arthromac® vs. Monovisc®)	
		M0	M4	P value	baseline	Post treatment
Arthromac®	Mean	1.93	0.9	< 0.0001*	< 0.01*	0.95
	SD	1.29	0.74			
monovisc®	Mean	3.93	2.3	< 0.0001*		
	SD	2.01	1.08			

Group		Womac score "activity "			P value (Arthromac® vs. Monovisc®)	
		M0	M4	P value	baseline	Post treatment
Arthromac®	Mean	11.9	6.33	< 0.0001****	0.818	0.48
	SD	2.63	2.87			
monovisc®	Mean	11.6	5.4	< 0.0001****		
	SD	3.59	2.44			

Note: *WOMAC: Western Ontario and McMaster Universities Arthritis Index
* Statistically significant p-value

4.Discussion

This study is the first of its kind to compare the efficacy of high molecular weight hyaluronic acid for two formulations in patients with knee osteoarthritis.

As with any other formulation, there were some undesirable effects. In frequent cases, the IA injections with HMW-HA were co-occurred with a sharp pain or knee oedema; furthermore, the practice per se includes the probability of causing septic arthritis.[17,18] these in turn cause local unwanted effects quite similar to those in other studies[19,20]

From such a perspective, the decline of knee pain along with the enhanced quality of life exceeds and offsets the high likelihood of transient flare-like symptoms.

Comparing the WOMAC pain scores after therapy to the starting point level, statistics show a remarkable enhancement in the absence of any notable dominance among the two injection types.

WOMAC stiffness in the study appears to have the most significant improvement. According to the final outcomes in this study, clinical achievement with one Arthromac® injection shows quite the same efficacy as numerous monovisc® during the time frame of 3 months of follow-up. Besides that, the two groups appear to not have any superiority.

Nevertheless, when comparing the method of manufacture, there is a difference. Arthromac®is manufactured by

biofermentation using yeast to obtain hyaluronic acid (linear type). Despite being a polymer and single injection, the amount diffused was significantly less, which made it less effective.

As for monovisc®, the manufacturing method is by means of bacterial fermentation lightly crosslinked, and this manufacturing method (cross-link) is a very common & crucial method that could be used to enhance mechanical elasticity, firmness, and stability of polymeric elastomers, mainly in H.A. These cross-links act as intersecting bridges that connect or bond two or more separate polymer chains together in order to form HA macromolecules with a greater size, higher Mwt, better density, and ultimately better performance.

The improved diffusion of the cross-linked HA could be described through the decrease in viscosity and the diminished size of the particle caused by the cross-linking.[21]Therefore, the methods of manufacturing or the source reveals an important role in the difference in effectiveness.

Even though these formulations produce proper pain relief along with better quality of life, unfortunately, it is still not considered a first-line therapy in osteoarthritis and traditionally reserved for second-line treatment.[22]

Regardless of all of the benefits mentioned above, there is an important factor that plays the key role in determining the type of treatment, which is the cost. And this is a negative point for both formulations, mainly monovisc®.

monovisc® is being administered as 3 doses (a month-long interval) per course in order to obtain the best outcomes (according to local Guidelines), yet because of its high cost, the cost of one injection is 330k IQD, i.e., the total is 990k IQD, people are satisfied with one dose for the purpose of temporary relief of pain and not an improvement in the disease. On the other hand, in terms of adherence, most patients who take monovisc® feel better after the first injection that they skip the second dose. And as mentioned above, monovisc® needs at least three doses until a clear improvement appears, and the interval between each dose is 6 months; this makes the Arthromac® superior in these prospectives (cost is 240k IQD and adherence as it is a single injection).

A Diversity of HA types and dosage forms are available on the market nowadays as a part of OA therapy. These formulations show some differences in their origin, molecular weight, structures, amounts, cost, course, and the injected volume. However, the vast majority of these HA preparations are multiple-injection regimens, yet some newer preparations have been formulated as a single injection and are gaining a lot of popularity nowadays. Zhang et al. Demonstrate the outcomes of individual and several injections of I-HA in KOA in a similar analysis and come up with a noteworthy conclusion that states individual injections were not subsidiary compared to several injections of HA in relieving pain and firmness and improving physical performance during approximately a 4- to 7-month period of time.[23] Baron et al. described similar outcomes, stating that a single HA injection showed a significant result as a therapy in knee osteoarthritis.[24]

This study has some limitations, candidates who were involved in the study were quite few and selected from a local area within one city which limited the Individual variation which in turn resulted in a limited results index. In addition, the short period of time of the study didn't show the full effect on long-term usage.

Conclusion & Recommendation

Both Arthromac® and monovisc® decrease WOMAC scores of the pain, stiffness, and physical function in knee OA patients compared with baseline. However, after taking the HA, WOMAC scores do not differ significantly between Arthromac® and monovisc® groups.

Further study is needed, which should be done on more patients for a longer time to have a clear result. Also, it is more precise to measure different biomarkers, e.g, osteocalcin (to reflect bone formation) or C-terminal telopeptide of type II collagen (to indicate cartilage degradation) to provide more accurate outcomes.

References

1- Braga L, Benner J, Nelson E. Description of individual radiographic characteristics of hip OA in African American and White male and female: the Johnston County Osteoarthritis Project. Arthritis Care & Research. 2010;62(2):190–197.

2- Baqer M, Mohammed M & Jassim N. (2020). Curcumin as an additional remedy to Meloxicam in the management of patients suffering from knee OA; Evaluation of antioxidant activity. Al Mustansiriyah Journal of Pharmaceutical Sciences, 20(1), 71–81.

3- Hannah Ritchie, Lucas Rodés-Guirao, Edouard Mathieu, Marcel Gerber, Esteban Ortiz-Ospina, Joe Hasell and Max Roser (2023) - "Population Growth" Published online at OurWorldinData.org. Retrieved from: 'https://ourworldindata.org/population-growth' [Online Resource]

4- Long H, Liu Q, Yin H, et al. Prevalence trends of site-specific OA during the years of 1990 and 2019: findings from the International Burden of Disease study 2019. Arthritis Rheum. Published online March 2, 2022. doi:10.1002/art.42089

5- Epidemiology of Osteoarthritis Zhang, Yuqing et al.Clinics in Geriatric Medicine, Volume 26, Issue 3, 355 – 369

6- I Haq, E Murphy, J Dacre, Osteoarthritis, *Postgraduate Medical Journal*, July 2003, Volume 79, Issue 933, Pages 377–383

7- Berenbaum F, Wallace IJ, Lieberman DE, Felson DT. Modern-day environmental reasons in the pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2018 Nov;14(11):674-681.

8- Delaware Valley Pain & Spine Institute.online: https://dvpainandspine.com/resting-for-pain

9- Hanada M, Takahashi M, Furuhashi H, Koyama H, Matsuyama Y. Elevated erythrocyte sedimentation rate and high-sensitivity C-reactive protein in osteoarthritis of the knee: relationship with clinical findings and radiographic severity. Annals of Clinical Biochemistry. 2016;53(5):548-553. doi:10.1177/0004563215610142

10- Altman R, Bedi A, Manjoo A, Niazi F, Shaw P, Mease P. Anti-Inflammatory Effects of Intra-Articular Hyaluronic Acid: A Systematic Review. CARTILAGE. 2019;10(1):43-52. doi:10.1177/1947603517749919

11- Gupta RC, Lall R, Srivastava A, Sinha A: Hyaluronic Acid: Molecular Mechanisms and Therapeutic Trajectory. Front Vet Sci. 2019 Jun 25; 6:192. doi: 10.3389/fvets.

12- Carmen G. Boeriu, Jan Springer, Floor K. Kooy, Lambertus A. M. van den Broek, and Gerrit Eggink, "Production Procedures for Hyaluronan," International Journal of Carbohydrate

Chemistry, vol. 2013, Article ID 624967, 14 pages.
13- Kendra Walker; Brandon M. Basehore; Amandeep Goyal; Patrick M. Zito._Hyaluronic Acid:National Library of medicine; StatPearls: July 3, 2023
14- Sillo O, Jackson k, Lopez L, Thomas E, Suhail A: WOMAC Osteoarthritis Index, physiopedia July 2013.
15- American College of Rheumatology. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). https://www.physio-pedia.com/WOMAC_Osteoarthritis_Index
16- S. S., E. (2011). The impact of chloroquine phosphate on C-reactive protein and ESR value in patients with knee OA. Al Mustansiriyah Journal of Pharmaceutical Sciences, 10(2), 1–8
17- Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation as a therapy for knee OA. Cochrane Database Syst Rev. 2006;(2):CD005321.
18- Ishijima M, Nakamura T, Shimizu K, Hayashi K, Kikuchi H, Soen S, Omori G, Yamashita T, Uchio Y, Chiba J, et al. comparasion between Intra articular hyaluronic acid injection and oral NSAID preparation in the therapy of knee OA. a multi-center, randomized, open-label, non-inferiority trial. Arthritis Res Ther. 2014;16(1): R18.
19- Raynauld JP, Torrance GW, Band PA, Goldsmith CH, Tugwell P, Walker V, Schultz M, Bellamy N. A prospective, randomized, pragmatic, health results trial estimating the incorporation of hylan G-F 20 into the treatment pattern administered for patients suffering from knee OA (part 1 of 2): clinical results. Osteoarthr Cartil. 2002;10(7):506–517
20- Kahan A, Lleu PL, Salin L. Prospective randomized experiment assessing the medicoeconomic benefits of Hylan GF-20 versus traditional therapy in knee OA. Joint Bone Spine. 2003;70(4):276–281.
21- Bodnár, Magdolna & Daróczi, Lajos & Batta, Gyula & Bako, Jozsef & Hartmann, John & Borbély, János. (2009). Preparation and characterization of cross-linked hyaluronan nanoparticles. Colloid and Polymer Science. 287. 991-1000. 10.1007/s00396-009-2061-9.
22- Reid, M.C. Viscosupplementation for Osteoarthritis: a Primer for Primary Care Physicians. Adv Ther 30, 967–986 (2013). https://doi.org/10.1007/s12325-013-0068-6.
23- Thabane L, Mbuagbaw L, Zhang S, Samaan Z, Marcucci M, Ye C, Thabane M, Giangregorio L, Dennis B, Kosa D, et al. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. BMC Med Res Methodol. 2013; 13:92.
24- Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee damage and osteoarthritis results grade (KOOS)-improvement of a self-administered result. J Orthop Sports Phys Ther. 1998;28(2):88–96.