

Efficacy Of Hyaluronic Acid And Corticosteroid Intra-Articular Injection In Knee Joint With Primary Osteoarthritis

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ABSTRACT

Background: Osteoarthritis OA is the most common joint disorder in the world. Injection of high molecular weight hyaluronic acid intra-articular with steroid is one of the used therapeutic option for patients with (OA)knee.

Objectives: Objective of this study was the evaluation the efficacy, safety, pluse duration of action of viscosupplementation of the HMWHA(high molecular weight hyluranic acid).

Type of the study: Cross-sectional study.

Methods: From 81 patients with sever knee pain due to OA (grades 3-4) were recruited from Al-Yarmouk teaching hospital & a private clinic during the period from January 2014 till July 2016. The patients were (24 males - 57 females) with mean age 57.14 years(range from 45y -64 y). Visual Analog Scale (VAS) questionnaire for pain, morning stiffness calculated by minuets and physical function were used to assess treatment efficacy after intra-articular HMWHA injection.

Results: The study included 81 patients who gave the examination data and complete the vital baseline and follow-up data necessary to check for the safety and

efficacy .Major improvement was seen after 6 months from injection, as pain, stiffness and physical activity data decreased to 20.32, 1.42 and 4.44 respectively. Such achievement continue for 9 months after injection, as the pain marks was 28.3, the stiffness marks was 3.15,while the physical activity marks was 5.

Conclusions: injection of HMWHA with steroid intr articular is effective, safe for the period of 9 months for those patients who complain from moderate and severe OA knee joint.

Keywords: osteoarthritis, hyaluronic acid, high molecular weight, intra-articular injection, viscosupplementation.

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Osteoarthritis (OA) of synovial joints is a clinical deformity in which there is increased softening and destruction of articular surface with a new growth of cartilage and bone at the marginal end of the joint called (osteophytes)with a cardinal sign's consist of :- (1) progressive cartilage destruction; (2) subarticular(sub chondral) cyst formation (3) sclerosis of the surrounding bone; (4) osteophyte formation; and (5) capsular fibrosis ,usually divided into 'primary' (when there is no obvious causing factor) and 'secondary' (when it follows a demonstrable trauma ,disease or joint abnormality) ⁽¹⁾. It is the most common joint disorder in the world and is the most common form of arthritis with obvious effect on the individuals activity and high social loss as loss of productive work time the knee joint consider one of the most affected joint by OA.⁽²⁾ Primary or idiopathic OA (as in this study), is of a polygenic nature i.e. a result from a complex interaction of biochemical and genetic factors. With significant risk factors . which include: Age ;usually in people above 40s years and increases with age. Gender more common in women than in men for most joints . Obesity . joint injury or disease or Joint abnormalities , Occupation: hard & heavy work can increase the risk of osteoarthritis in some joints. Diabetes type 2: was found to be a factor that effect the development and progression of knee OA^(3,4,5),the pathogenesis & pathophysiology of OA is a complex matter that affects different systems, starting with the articular cartilage and in its content of chondrocyte &

water that help in regeneration and mentainenc the cartilage content. The water amount around (65% - 85%) of the cartilage substances in addition there is interaction between hyloronic acid, matrix proteoglycans, matrix collagens, hyaluronic acid, plus other components and all these substances contribute to articular cartilage health ,in general the cartilage survival is a balanced process between matrix synthesis and matrix degradation ,,in OA matrix degradation is faster than matrix synthesis ⁽⁶⁾.

Signs and symptoms like Pain, Stiffness , Swelling , varus deformity , local tenderness , limping , restriction & progressive limitation of daily activity with Crepitus during joint movement ,Instability due to loss of articular cartilage & bone, asymmetrical capsular contracture and/or muscle weakness ^(7,8), diagnosis by history and clinical examination, X-rays finding , while the aim of management is to relief pain , improve function & mobility of the joint ,it usually started by personal education physiotherapy &exercise's this is (non-pharmacological measures) next line in treatment is the pharmacological non-steroid anti-inflammatory drugs , then next measures in the management is the intra-articular injection either local steroid injection or recently haylarunaic acid injection final stage is the surgical measures as laparoscopic washing ,high tibial osteotomy or total knee replacement ^(9,10,11)The synovial fluid is about 2 ml in which a hyaluronate concentration of 2.5 to 4.0 mg per milliliter it is produced by type B synoviocytes , fibroblasts of the synovial membrane and chondrocytes ,the ((Hyaluronic

acid (HA) is a high-molecular-weight mucopolysaccharide), naturally seen in living organisms with extraordinary biological (rheological) properties (pertaining to the deformation and flow of matter) which enabling it to act as a lubricant or shock absorber, depending on the forces applied on it^(8,9, 10). i.e the Synovial fluid act as lubricant in slow movement (e.g. in walking) & act as elastic shock absorber in rapid movement (e.g. in running), also as act nutrition medium, that transmit cellular signals to articular cartilage^(12,13,14). (HA) not cytotoxic with good biocompatibility also non-antigenic & non-immunogenic^(15,16,17). The American College of Rheumatology (ACR) guidelines, Recently updated guidelines include recommendations for the use of intra-articular hyaluronan^(18,19) mainly in the treatment of acute exacerbation of painful attack in an OA knee joint. research's found that HA help chondrocyte proliferation and differentiation, so it can be used as a scaffold component in tissue-engineering techniques, the concentration and molecular weight of HA usually decreased by 33% - 50% in OA joint leading to decrease its role in preserving normal joint biomechanics & functions^(20,21) because of its viscoelastic nature and the ability to form highly hydrated matrices, it have a high Chondroprotective effects & plays a major role in the development of cartilage, the maintenance of the synovial fluid and the regeneration of tendons in summary. In the OA knee joint there is a decrease in synovial fluid elasto-viscosity, synovial fluid HA concentration, and the molecular weight of HA^(22,23). This will decrease absorption of shock ability, decrease lubrication, and impair joint protection by the synovial fluid. HA injection intra articular treatment is aimed mainly in getting a good viscoelastic properties of synovial fluid that decrease the painful elements of OA joint^(24, 25,26). Specially when the joint is not responding any more to the traditional NASD's & physiotherapy after injected HA in the joint it is cleared in less than one day, but its advantage from single injection may stay several months⁽²⁷⁾. that was postulated through stimulation of de novo HA synovial synthesis, suppression of cartilage matrix degeneration, and suppression of inflammatory responses to interleukin-1.^(27,28,29, 30)

Methods: At Al-Yarmook teaching hospital and from private clinic, ((81 eighty one)) participants with an age range from (45y- 69y) with mean age of 57.14 years. Females \ male ratio is (3\1) [males = 24 (28.4 %), females = 57 (71.6 %)] were suffering from moderate to sever OA between the periods from January 2014 to July 2016, in whom we decided to start treatment with intra-articular HA injection, following them by screening & analysis the observation result from baseline assessment (day of injection) to 9 months period. The case report questionnaire were included for each participant's demographics and related medical history, an erect position X-ray were taken for both the knee joint, with the foot adjusted as the second metatarsal bone parallel to the X-ray beam, these radiograph were obtained as a baseline on the first visit and then were analyzed according to Kellgren-Lawrence (KL) scale for the

presence of OA as follow :- (normal= 0), (doubtful OA=1), (minimal OA=2), (moderate OA=3) and (severe OA=4). All data & patients measures analyses were performed from -baseline & follow-up at 1 month, thired months, sex months and nine months post-injection

The inclusion criteria : Patients with an age older than 45 years with OA of the knee in the femoral-tibial joint, either unilateral knee or bilateral with OA according to (Kellgren-Lawrence grade III and IV), as check by the x-ray and a minimum pain score ≥ 30 on both knees as assessed by Visual Analogue Scale (VAS) 0-100 mm, (0 = no pain, 100 = very severe pain). They were symptomatic complaining for at least 6 months they Reported pain most of the times days & night for the previous 3 months they had no or limited response to non-pharmacological therapy or they couldn't tolerate NSAID therapy taken regularly in adequate dosages for long time.

Patient Preparation;- Full exposure the diseased knee joint on supine position with the knee extended with an absorbent pad placed beneath the it.

Equipment's :- Sterile Tray for the Procedure cover by sterile sheet with the following items inside (fig.1): Sterile gloves, sterile fenestrated drape, two syringes (10-20mL), two (18-21 gauge) needles, gauze soaked with povidone-iodine solution (Betadine), 5ml. of 70% isopropyl alcohol solution, sterile crepe bandage.



Figure 1. Sterile kit for injection

Procedure Description:- patient is supine with the knee extended on the couch. from the lateral side The synovial cavity was approached (medial approach also can be used) as to drain a synovial fluid effusion if present

1. The lateral superior border of the patella is detected. The site was sign with a pen, now (1 cm) above and (1 cm) lateral to this sign, is the site that give the most accessible pathway to the synovial space.
2. local anaesthetic Applied by Ethyl Chloride spray to skin of the affected knee, then washed by povidone-iodine

solution , isopropyl alcohol solution 70% for disinfection was applied to complete sterilization .

3. Then a needle of 1-inch length & 21-gauge of size , with 10ml or 20-ml syringe attached , according to the expected synovial fluid for aspiration is inserted through stretched skin. that help reducing needle-insertion discomfort by Stretching the pain fibers in the skin with the non-dominant hand , the needle should be directed at 45-degree angle distally into the knee, pushing it beneath the patella.
4. Insertion of the needle to a distances of 1-4 cm , performing an aspiration of synovial fluid to decompress the knee joint cavity and remove as much as possible from the in the synovial fluid with its catabolites precipitate so it decrease pain also aspiration will prevent dilution of the injected HA.
5. Once the syringe has filled, it should be evacuated with great care not to injury the articular surface by the needle tip , then a new syringe contain Methyl-prednisolone (depo- Medrol 40-80 mg.) corticosteroid drug 1-2 ml. mixed with 3cc of (xylocaine 2% concentration) with out adrenalin attached to the needle & injected to the synovial cavity .



Figure 2. Aspiration of synovial fluid

6. Another new syringe filled with 3 ml HA will then replace the empty corticosteroid syringe will be attached to the same needle inserted . and a gentle injection of the drug performed , then we withdraw both the syringe & the needle .
7. Then skin sterile by iodine povidone, and an elastic crepe bandage is applied for 24 hours over the site of the needle-puncture , involving whole knee joint.
8. The patient stay in a supine position for few minutes with the injected joint moved passively in flexion & extension in order to spread the injected

amount of HA across the synovial space to decrease the friction problem

9. A knee splint was then applied to the injected knee.
10. The patient then advised to avoid forceful activity of the joint for the next 48 hours
11. patients were advised to take oral antibiotic for 5 days With local ice pack on site of injection to ease the pain of needle puncture painkiller , was allowed for pain management. The following clinical parameters were used to assess treatment efficacy and were evaluated at baseline visit, 1month, three months, six months and nine months after intra articular steroid with HA injection:

Visual analogue scale (VAS): by measuring the distance out of 100 mms representing the magnitude of pain that the patient may suffer.

Morning stiffness: measured by estimating the time taken by the stiffness to be ended with in (5, 10, 15, 20, 25, or 30 minutes).

Physical function: The physical function scale included questions about the degree of difficulty when: rising from sitting, walking on flat, getting on / off toilet, ordinary light domestic duties. Each of the 4 questions is graded upon a five-point scale (0 to 4) (0: not any, 1: a little, 2: moderate, 3: sever 4: very sever - extreme)

Result ;- Analysis of pain, stiffness and physical function, with baseline assessments of demographic data and relevant medical history (e.g. of Diabetes mellitus, Hypertension or cardiovascular diseases) was done and the results was documented and reported the study included 81 patients who agree to the procedure & completed all visits. The mean age of the participants was 57.14 years. Females \ male ratio is (3\1) [males = 24 (28.4 %), females = 57 (71.6 %)]. Each participant was screened for the following data :Age, sex, occupation, weight, height, BMI, side of the affected knee, radiological severity, duration of complaint from OA in months, DM ,HT, CVD, in addition to VAS ,stiffness and physical function scores. Participant demographics and baseline characteristics are listed in Table 3.1 And Figure 3.1, 3.2, 3.3, & 3.4 respectively.

Statistical analysis of the efficacy of intra-articular HA

injection: Each participant was assessed & compare with there baseline visit then

(1 month, three months, six months, nine months) after administration of HA intra-articular injection. With each visit, three main questions were answered:

- a- the level of pain for each knee,
- b- the time taken for the morning stiffness to resolve,
- c- the degree of difficulty in doing physical daily activities

The pretreatment scores mean for pain were 58.42 (total score of 100),, for stiffness were 10.43 (total score of 30), and for functional performance were 12.48 (total

score of 16), respectively. At the first month post-injection ,the improvements was statistically significant in VAS according to pain, stiffness, and daily functional performance were detected , as these scores improved to for pain (34.99), for stiffness (5.19), and for function(6.42), respectively after HA injection administration. analysis of improvement was at its peak on sex months after HA injection administration, as the scores result for pain, , functional performance and stiffness had decreased to(pain score - 20.32), (function score4.44) and (stiffness score - 1.42), respectively.After 9 months of the injection ,still a Significant improvement was elicited, as showing by a (pain score of 28.3), (functional performance score of 5.) and a(stiffness score of 3.15), The decrease in the rates of pain, , difficulty in performing daily physical activity and stiffness were statistically and clinically relevant. The results were elicited in Table 2 and Figure 5. For the analysis of the pain scores obtained from the questionnaire. While that for stiffness the results of the analysis of the scores obtained from the questionnaire are presented in Table 3 & Figure 12.And that for physical function difficulty , statistical analysis results scores are resented in Table.4 and Figure 13. Complication include :- Pain at the site of injection, redness and swelling, may be observed., 21 patients complain from pain alone, 9 patients complain from redness with pain at the knee joint, 3patients complain from swelling with pain , lastly 2 participants suffered from continuous pain, redness and swelling, plus restricted flexion movement of the knee joint .. these previously mentioned local side effects (which are treated symptomatically by ice pad applied locally , pain killer& NSAID's) lasted no longer than 72 hours and the treatment was not interrupted in any of these cases, there were no general complication like anaphylactic shock or allergic reaction from the injection in all our patients .These results confirm the safety and tolerability of intra-articular HA injections with out any sever side effects. as the main side effects were mainly local, such as mild pain, local redness, and transit swelling at the site of administration of the intra-articular HA injections



Figure 4. Injection of knee joint with HA.

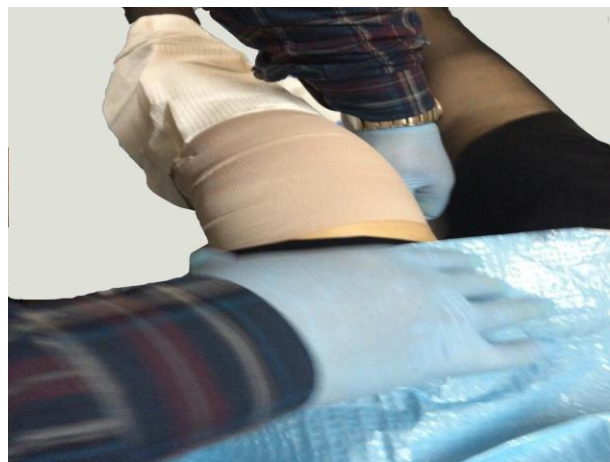


Figure 5. Bandaging of Knee joint.

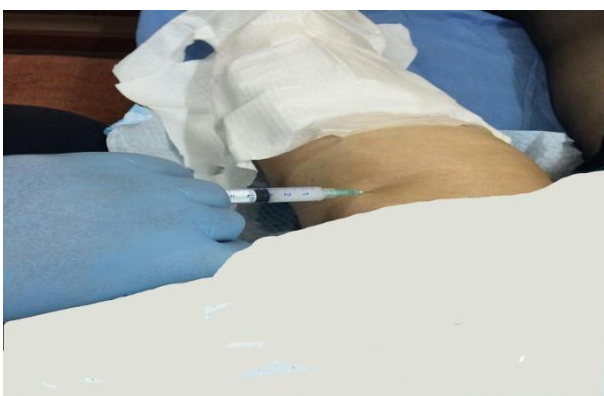


Figure 3.Injection of the knee joint with steroid



Figure 6. Post injection : moving of the knee joint.

Table 1: Patients demographic data.

variable	Mean (SD) or percentage
Age	57.14 (6.97)
Sex	Male (28.4 %),Female (71.6 %)
Weight	73.61 (7.65)
Height	168.16 (2.88)
BMI	27.84 (2.95)
Affect knee	Right (30.9 %), Left (39.5 %), Bilateral (29.6)
Radiolog. Severity	Severe (28.4 %), Moderate (71.6 %)
Duration - month	10.62 (4.47)
Occupation	Teacher(23.5%),Housewife(40.7%), Farmer(21%),Employee(14.8%)
DM,HT,CVD	53 %

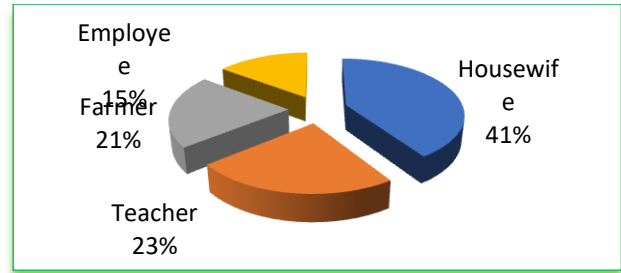


Figure 10: The patients demographic data.

Table 2: VAS results with the corresponding visit

Visit	Time (month)	Mean	SD	t-value	P-value
Baseline visit	0	58.42	7.86	-	0.000
1 st visit	1	34.99	11.43	26.048	0.000
2 nd visit	3	25.06	10.26	42.809	0.000
3 rd visit	6	20.32	7.52	64.128	0.000
4 th visit	9	28.3	8.25	43.716	0.000

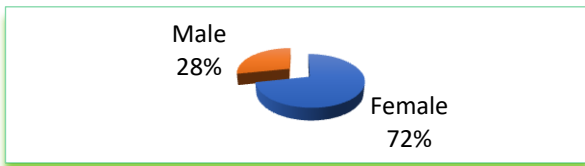


Figure 7: The patients demographic data.

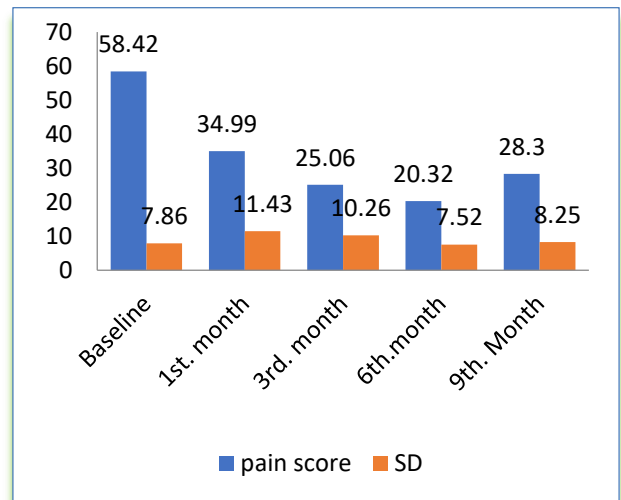


Figure 11: VAS results with the corresponding visit.

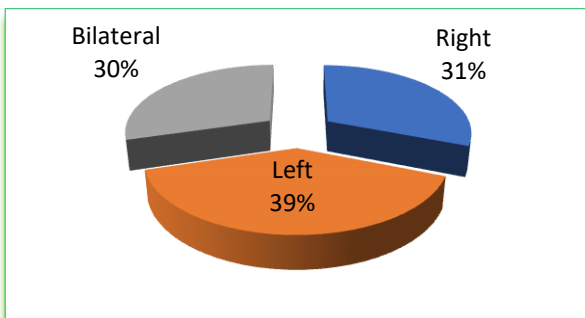


Figure 8: The patients demographic data.

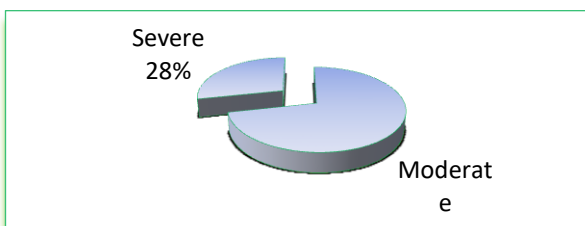


Figure 9: The patients demographic data.

Table.3: Stiffness scores results with the corresponding visit.

Visit	Time (month)	Mean	SD	t-value	P-value
Baseline visit	0	10.43	3.88	-	0.000
1 st visit	1	5.19	3.9	43.32	0.000

2 nd visit	3	2.16	2.49	31.11	0.000
3 rd visit	6	1.42	2.27	30.36	0.000
4 th visit	9	3.15	3.3	20.7	0.000

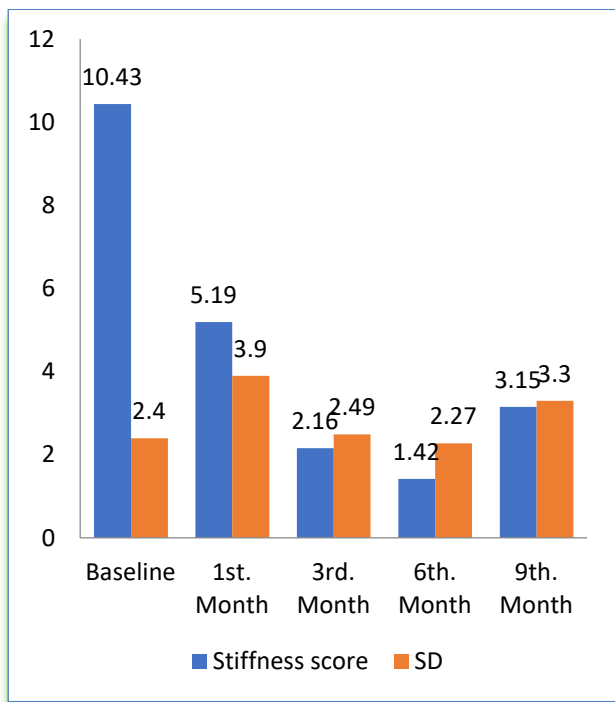


Figure 12. Stiffness scores results with the corresponding visit.

Table 4. physical function scores with the corresponding visits.

Visit	Time (month)	Mean	SD	t-value	P-value
Baseline visit	0	12.48	2.1	-	0.000
1 st visit	1	6.42	1.97	41.81	0.000
2 nd visit	3	4.85	1.73	52.1	0.000
3 rd visit	6	4.44	1.41	51.37	0.000
4 th visit	9	5	1.75	43.41	0.000

Discussion Painful knee joint due to mild, moderate or severe OA of the knee joint in an old patients with ischemic heart disease, hypertension, DM & peptic ulcer is one of the most common & difficult problems that the orthopedic specialists face in the daily clinical practice, it is a challenge in the management regimens, as most of these patients are unable to take or tolerate NSAIDs for a long time, and they hesitate, refuse or has a contraindication to do knee surgery. In such a situation we found that intra-articular injection of high molecular weight hyaluronic acid (HMWHA) with long acting steroid & local anesthetics of 2% Xylocain may be the possible answer to relieve an acute painful attack of an OA knee it also help to improve movement & decrease stiffness of the

knee joint for a period of time this proved in a prospective study of 81 patients with moderate to severe OA of the knee joint that cause an annoying persistent pain & limitation of knee function, as they get no benefit from non-pharmacological treatment methods and they show limited response to acetaminophen or NSAIDs or they were unable to keep taking these medications for long time repeatedly. this was agreed by struss et al, by Conrozier T. et al, & by Brockmeier SF. & Eric J. Strusset al. (31,32,33,34)

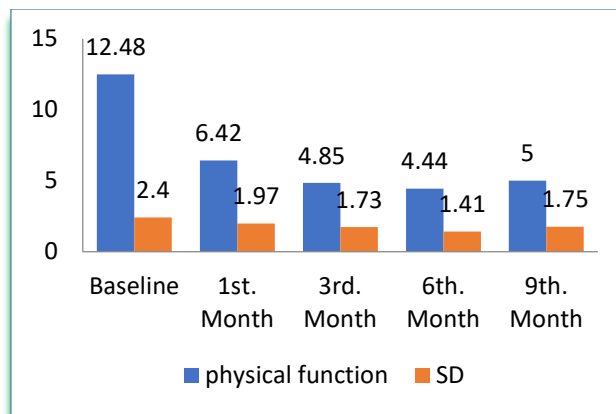


Figure 13. physical function scores with the corresponding visits.

In this study we found that patients with moderate OA knee joint respond well to such intra-articular injection with steroid than patient with severe OA, this result was approved also by David Zelman (35) research who stated that hyaluronic acid injections seem to work better in some patients than others & with much less effectiveness in older adults with severe OA. Changes. Robert J Petrella (36) report that the improvement degrees in both mobility and pain were greater significantly than that achieved in matched groups of patient treated with only OA drugs without HA & steroid injection. Intra articular injection, this is similar to a result in our study were patient with HA & steroid injection get better improvement than patient on NSAIDs only. In addition, HA Injection are safer than NSAIDs and COX-2 inhibitors from gastro-intestinal & cardiovascular point of view as HA usually safe and not complicated with major GIT problems of NSAIDs or with major CV. system side effect of the recent selected COX-2 medication. This was stated by Timothy Gower (37) in his study he report that HA injections are the treatment of choice when a patient get no benefit with non-steroidal anti-inflammatory drugs (NSAIDs) to control pain, and in a patient's who don't tolerate these drugs (with its side effects such as stomach bleeding and kidney problems).

In our study, we use methylprednisolone as an adjuvant agent at the same time with HA. Egemen Ayhan, et al, (38) mention that the IA corticosteroid injections provide short term reduction in OA pain and can be considered as an adjuvant to core treatment for the relief of moderate to severe pain in people with OA. besides steroid will decrease clinical inflammatory sign & symptom of the affected joint as erythema, swelling, heat, and tenderness it also relatively increase in viscosity & an increase in hyaluronic acid (HA) concentration.

The data of the patients were showing the relationship between aging and OA, this fact was so obvious with participants mean age of (57.14). Thomas H'ugle, et al, (39) has documented that aging alters the musculoskeletal system of the human body on functional and a molecular levels. As the age has an effect on Cellular matrix modification & renewal, with decreases in the immune senescence & the capacity of regeneration of connective tissue in general, & specially that of cartilage & bone That emphasis the role of the aging factors of in the appearance & deterioration of OA. The demographic data show that females are more affected with knee OA than males. Giuseppe Musumeci, et al, (40) documented that several epidemiologic studies of OA suggest the relevant difference between pathological pathways occurring during the onset of this disease in males and females were women usually show a higher prevalence of OA of the knee than men specially after menopause, the prevalence of OA in women significantly increases this observation suggests that hormonal factors could influence progression and development of the disease, the disparities may also be dependent on the difference in the structure of bones and ligaments, such as strength and alignment, laxity of ligaments, besides the reduced volume of cartilage in women compared with that of men. In fact, approximately 9.6% of men and 18% of women show symptomatic OA. The data results also demonstrate the effect of occupation in the OA development. Messier, et al, (41) document that in OA, two aspects must be considered: repetition of movements of the knee joint and their wrong execution. The first aspect reflects the development of OA in people who in their daily work & activity or occupation are forced to do repetitive movements of knee joint as flexion & squading, these patients have a double risk of developing localized OA in comparison with people whose employment does not require physical activity and repetition of the same movement

The data of BMI with a mean of 27.84 indicate that patients with over-weight were more susceptible to the development and progression of OA, as the knee joints were bearing heavy weight all over the standing and walking times. Such a result also stated by Blagojevic M (42) who report that Obesity is a recognizable risk factor for developing knee OA. Several large number of studies have directly correlated obesity with the knee OA. A meta-analysis of these studies also demonstrated that there is an almost three fold increase in the risk of developing OA within an obese or overweight population. In a study done by Gorman and Krook, (43) the prevalence of osteoarthritis in type 2 diabetic patients was found to be significantly higher than the estimated prevalence in the general population. In a large study on osteoarthritis including 1026 patients, the mean fasting glucose concentration was higher in subjects with osteoarthritis than in subjects without OA. This result were clearly shown in the relevant medical history data were clearly explain the relation-ship between DM and OA, as 37 % of the participant in our study were diabetic .On the other hand 57% of the patients in our study were affected with either DM, HT or CVD disease with high risk of complications when they use NSAIDs for long time or depend on repeated steroids injection as a main line of OA management. The results of our study may put the HA as a 1st line of treatment together with non-pharmacological measures in patients with DM, HT and CVD.

Vibeke Strand (44) conclude that intra-articular injection of (FDA approved)viscosupplements is safe and efficacious through 26 weeks in patients with symptomatic knee OA. In this study, although the peak improvement were recorded at the 6th month after administration of HA, the 9th month results of pain, stiffness and physical function scores also show significant improvement (clinically and statistically) with the P-value showed very highly significant difference (P-value =0.000) and the t-value at 9th month were showing for (pain 43.72),(stiffness 20.7), and for (physical function43.41), due to the use of HA intra-articular injection . We depend mainly on high Molecular Wt . cross linked HA . which was found by many authers like Michael J. Daley (45) who reported that chemical cross-linking techniques in preparing HA ,prolong its residence time following injection; which may promote longer duration of action. Demirhan Dıraçoğlu (46) documented that Single injection of high molecular weight, tightly cross-linking HA seems to be as effective as three injections of standard HA in patients with knee OA. Single time injection of HA's advantages have a short time for application and being more comfortable treatment for the patients. Furthermore, increasing injection number may lead to increase the risk of local complication & adverse effects example. bleeding, septic arthritis or allergic reactions).

Conclusion: In conclusion, our results were encouraging for the use of HMWHA and steroids as an alternative and an adjunct treatment to oral analgesics in patients with moderate to severe OA of the knee joint..The efficacy and safety of intra-articular HA administration demonstrates that the viscosupplementation is a valuable and safe treatment option for OA of the knee.

Recommendations: Future randomized trials should be carried out with larger sample sizes and longer duration to identify optimal treatment options for patients with OA of the knee.

Studies should be carried-out to evaluate whether there are synergistic effects of combining a HA product with steroids and current products used for treating patients with OA

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